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Section of Anæsthetics

President—Professor R. R. MACINTOSH, M.A., D.M., F.R.C.S.Ed., F.F.A.R.C.S., D.A.

[*January* 1, 1954]

THE PRESENT POSITION OF SPINAL AND EXTRADURAL ANALGESIA [*Abridged*]

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Spinal Analgesia

"THE statistical fact that spinal analgesia is three times as lethal as the condemned chloroform anæsthesia of fifty years ago is one to make the thoughtful ponder the deadliness of the technique so nonchalantly exercised" (Editorial, *Anesthesiology*, 1950). This statement is characteristic of attacks on spinal analgesia in that it is prejudiced and based on out-of-date figures. The statistics (Corlette, 1946) are highly selected, larger, favourable series being ignored, and in 1950 were at least eighteen years old.

It is probably true that the most certain way to have a death on the table is for someone inexperienced in the method to give a spinal to an unsuitable patient. This has happened many times in the past and as a result the method has been stigmatized as dangerous; it is dangerous when used in that fashion. Wayne Babcock, who had an enormous experience of spinal analgesia, stated that after a death from spinal anæsthesia the anæsthetist may often properly write his own name in the space reserved on the certificate for the cause of death.

In discussing the sequelæ of spinal analgesia it is convenient to consider first those associated with the lumbar puncture and second those which may be associated with the introduction of the analgesic agent.

COMPLICATIONS OF LUMBAR PUNCTURE

The complications of lumbar puncture fall into three groups (Dripps and Vandam, 1951):

Group I.—Complications associated with disturbance of the dynamics of the cerebrospinal fluid (C.S.F.). This disturbance is due to the prolonged leakage of C.S.F. from the subarachnoid to the extradural space (Franksson and Gordh, 1946). It is generally accepted that the most common type of post lumbar-puncture headache, i.e. the headache aggravated by the erect posture, falls into this group (Editorial, *Lancet*, 1953). The use of fine needles coupled with adequate hydration of the patient can reduce the incidence of this type of headache to less than 3% (Southworth and Hingson, 1953). In the rare intractable headaches the extradural injection of saline has been shown to be a worth-while procedure (Rice and Dabbs, 1950).

Bryce-Smith and Macintosh (1951) have given support to the theory that the VI nerve palsy which can follow lumbar puncture and spinal analgesia also falls into this group. The reported incidence following spinal analgesia varies widely, from once in 202 cases (Fairclough, 1945) and once in 400 cases (Thorsen, 1947), to twice in 1,581 cases (Kennedy and Lockhart, 1952). Measures taken to reduce the incidence of headache should also prove effective with this complication of which over 90% clear up in eight weeks or less; occasionally recovery is delayed for several months and, very rarely, paralysis is permanent.

Group II.—Complications associated with traumatic and inexpert lumbar puncture. According to Dripps and Vandam (1951) paralysis and weakness of muscles, usually in the legs, has followed lumbar puncture. Bromley *et al.* (1949) reviewed 44 cases of injury to the intervertebral disc following lumbar puncture; however, the great majority were in children. Provided lumbar puncture is performed in the lower lumbar region with a suitable needle and with reasonable care the spinal cord and the constituent nerve roots of the cauda equina should escape damage (Macintosh,1951). The introduction of blood or epithelial cells into the C.S.F. may produce a meningeal reaction which is an occasional cause of headache.

Group III.—Complications associated with infection, either localized or diffuse, due to septic technique or the introduction of the needle through infected skin. Garrod (1946) stated that there is good evidence for believing that many cases of "aseptic" meningitis following spinal anæsthesia are

due to infection of the spinal canal by Gram-positive bacilli of types found in water used for rinsing syringes and needles and that the presence of such bacteria is not necessarily detected by ordinary methods of C.S.F. examination. Thorsen (1947) gave the incidence of purulent meningitis as one case in every 800 cases of spinal analgesia. This should be a completely preventable complication and many large series have been reported with no cases.

Complications which may be Associated with the Introduction of the Analgesic Agent

These include transient and permanent cauda equina lesions and cases in which the lesions extend higher and are usually a combination of radiculitis, cauda equina lesions, ascending myelitis and adhesive arachnoiditis. Neither the cause nor the incidence is known with certainty and there is dispute about both.

The incidence.—Kennedy *et al.* (1950) state that unfortunately it is not generally known, and still less widely accepted, that spinal anæsthesia may result in temporary and permanent neurological complications. This sweeping statement can only be applicable to very few anæsthetists. It is also often suggested that the reported incidence of these complications is less than the true incidence because (1) anæsthetists do not look for them, and (2) the onset is often delayed for months. However, it is clear from case reports (Ferguson, 1937; Kennedy *et al.*, 1950; Bergner *et al.*, 1951) that in the great majority of cases there is an early onset of symptoms of sufficient severity to suggest to the most casual observer that something has gone wrong.

The causation.—Because cases have been reported in which there was no evidence of infection and because in bacteriologically confirmed cases of purulent meningitis there was no evidence of cauda equina lesion, it is unlikely that infection following spinal analgesia can be the cause of these lesions. It has already been seen that trauma is also an extremely unlikely cause.

It is known that the intrathecal introduction of any foreign substance produces an aseptic meningeal reaction characterized principally by pleocytosis and increased protein content. Therefore the causation of the lesion following spinal analgesia very likely lies with the injection of the spinal analgesic agent or some other substance accidentally introduced.

As far as post-spinal cauda equina lesions are concerned, Dinsdale (1947) stated that all the recorded evidence of the causation incriminated the use of concentrated solutions (such as procaine 10% and Stovaine 10%) which are kept in contact with the sacral roots for a long period. This evidence included the experiments of Macdonald (1937) who showed that in cats the intrathecal injection of increasing concentrations of procaine were associated with an increasing incidence of permanent cauda equina lesions. However, he found that to obtain these symptoms he had to use doses of procaine of about five times the usual clinical dose calculated on equivalents in terms of body-weight.

Eversole (1949) stated that there is increasing evidence that post-operative neurological changes may bear a direct relationship to the concentration of the anæsthetic drug in the subarachnoid space and that we may expect a lower incidence of these complications when lower concentrations of these drugs are used. It is clear, however, from case reports that lesions of the spinal cord can follow the use of all the commonly used concentrations of the various drugs including 1/1,500 Nupercaine (Hewer, 1933) and that though excessive concentrations are very likely, as one would expect, to prove harmful this is not the cause in all cases. Some other factor must be involved.

It is the belief of most neurologists (e.g. Kennedy *et al.*, 1950; Critchley, 1953) that these complications are almost certainly due to the direct action of the various analgesic drugs used though there is disagreement over the specific mode of action. The commonly expressed argument is that the neurological complications of spinal analgesia occur in those regions of the central nervous system situated most closely to the site of injection of the anæsthetic agent. This is true enough. But it does not explain why only a small proportion of cases following spinal analgesia show evidence of damage or the occurrence of damage in patients who have previously, in some cases years before, had spinal analgesia, often with the same agent, on one, or even two occasions without damage (Martel, 1952; Medicine and the Law, *Lancet*, 1953). Nor does it explain why a technique and drug which is successfully used in hundreds of cases is followed by a small group of cases of damage all occurring within a short period of each other.

It is suggested that contamination of ampoules of the analgesic agent with irritant sterilizing solutions, a hitherto minimized cause of the damage, offers a satisfactory answer to the problem raised (Sise, 1931; Nicholson and Eversole, 1946; Macintosh, 1951).

Macintosh (1951) strongly recommends autoclaving not only to reduce the risk of infection but also to abolish the risk of contamination.

After a recent hearing (Medicine and the Law, *Lancet*, 1953) Mr. Justice McNair decided that two cases of severe paralysis following spinal analgesia with Nupercaine must have been due to the injection of phenol in which the ampoules had been stored. As the injections were made six years ago he decided that the defendant anæsthetist could not be held to be negligent. It is clear, however, from his remarks that in any future case if it is found that ampoules have become contaminated in this fashion the judgment might easily be very different.

It is believed that the contaminating agent either alone or occasionally in conjunction with the known irritant action of the more concentrated solutions of analgesic drugs may be responsible for the majority of cases of paralysis. If this is so, then the practice of autoclaving ampoules should reduce the incidence of paralysis to negligible proportions.

It is widely believed that the onset of symptoms in latent disease of the central nervous system may be precipitated by spinal analgesia and that quiescent or active pre-existing disease may be worsened. It is therefore wise not to use spinal analgesia in patients with known or suspected disease of the central nervous system.

Methods.—In addition to single dose spinal analgesia, technically more difficult and complex continuous methods are available which allow a greater control of duration and height of analgesia and dosage of drugs. Southworth and Hingson (1953) state that wherever spinal analgesia is indicated the continuous segmental method of Saklad is the method of choice. Dripps (1950) on the other hand, considers that continuous methods should be used less frequently because of the impression that there is an increased incidence of headache, diplopia and other neurological sequelæ. In any event it is clear (Dawkins, 1953) that segmental extradural block possesses all the advantages without the disadvantages of segmental subarachnoid block and should be used in preference.

Indications.—Because of unexpected deaths due to improper application of the method and because of occasional serious neurological damage due largely to imperfect technique spinal analgesia has never been widely popular. It was used by many as an imperfect substitute for deep general anæsthesia for the production of relaxation. When the competent use of the relaxants plus light general anæsthesia is available the production of relaxation can no longer be the sole criterion for the use of spinal analgesia because of the occurrence, rare though it may be, of neurological damage.

However, spinal analgesia possesses other advantages which should prevent it from being regarded as a relic from the dark ages of anæsthesia and which indicate when it may properly be employed. Advantages over light general anæsthesia plus relaxants are the production of contracted bowel and the reduction of hæmorrhage. With low spinal blocks there is the minimum of disturbance to metabolism and vital functions. The risk of aspiration of stomach contents associated with general anæsthesia but which, it is agreed, can be minimized by correct technique applicable in most types of emergency anæsthesia, is not associated with unsupplemented spinal analgesia. Of all methods of regional analgesia spinal is the simplest to produce, the most likely to be effective and therefore the least likely to require supplementary anæsthesia. Apart from simplicity of production extradural block possesses all the advantages of spinal analgesia without the disadvantages of headache, diplopia and risks of intrathecal infection and may be used equally well except when a rapid onset of analgesia is required.

(1) *Abdomino-perineal resection of rectum.*—Jarman (1953) states that in the majority, if not all, cases of abdomino-perineal resection he uses spinal analgesia. He has used relaxants but he has no doubt that the spinal cases have a better convalescence than the patients who have relaxants.

(2) *Prostatectomy.*—Wells (1953) discussing Wilson Hey prostatectomy considers that spinal analgesia is almost obligatory and doubts whether deliberate and satisfactory hæmostasis by diathermy can be achieved under general anæsthesia. Low spinal block combined with infiltration of the abdominal wall is an excellent method for poor risk cases with really bad chronic bronchitis and emphysema.

(3) *Amputation.*—In similar poor risk cases requiring major amputation in the lower limb low spinal analgesia has given excellent results in some twenty cases.

(4) *Operative obstetrics.*—Many recent reports of large series indicate that spinal analgesia, correctly used, is not a factor in the production of maternal mortality (Thorne, 1952). Malkin (1953) describes 1,180 consecutive Cæsarean sections between 1947 and 1951 with only one maternal death and that not attributable to the spinal. Spinal analgesia has long been known as the protector of the baby. However, properly given, general anæsthesia is not harmful to the fœtus except, possibly, when the fœtus is very premature or distressed; in particular, light general anæsthesia plus relaxants gives excellent results (Davenport, 1951; Thomas and Gibson, 1953). General anæsthesia, however, exposes the woman in labour to the risk of aspiration of stomach contents (Thorne, 1952). Jeffcoate (1953) states that the greatest danger of forceps delivery at the present time is anæsthesia and that this danger has, if anything, increased with the introduction of modern anæsthetic agents whose safety depends on increasing skill on the part of the anæsthetist, and that since 1950 at the Liverpool Maternity Hospital there have been cases of inhalation asphyxia and pneumonia as a result of vomiting during induction or recovery from anæsthesia. The possibility of regurgitation is especially present when relaxant drugs are used and Morton and Wylie (1951) have described certain essential precautions to avoid this risk. Thomas and Gibson (1953) describe 290 cases of forceps delivery with relaxants with 18 vomiting or regurgitating, fortunately without serious sequelæ, in which apparently the recommended precautions were not taken. It may not always be feasible to take these precautions, at any rate in forceps delivery, and without them surely the method is dangerous. Spinal analgesia prevents all risk of aspiration and

in our experience of over 500 cases in operative obstetrics, including 351 cases of forceps and 148 cases of Cæsarean section, has been completely satisfactory. The only complication, headache in 11%, has caused concern in only 7 cases. Andros (1953) has made an exhaustive review of the effects of spinal analgesia on all aspects of labour.

(5) *Hypotension.*—This has been fully discussed by Griffiths and Gillies (1948) and Gillies (1953).

Conclusion

Even if it is believed that the neurological sequelæ of spinal analgesia can be reduced to negligible proportions, in which chance is the main factor, the risk exists and therefore spinal analgesia should never be used routinely but only when indicated.

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The Present Position of Sacral-extradural Analgesia

Nomenclature.—Ten years ago the nomenclature of extradural analgesia was in a muddle and at a similar meeting to this I ventured to suggest that the term "peridural" should be replaced by "lumbar and thoracic extradural" and that the term "caudal" should be replaced by "sacral-extradural" (Galley, 1945). It is satisfying to note that these suggestions have taken root as the nomenclature now used makes it clear that both types of extradural (epidural) analgesia are essentially the same and merely differ by virtue of the approach made to the extradural space.

Technique.—On no account should increasing familiarity with the technique of sacral-extradural analgesia lead to the abandonment of the "test dose". If the needle is properly placed the test dose with the older drugs produces little or no skin analgesia but it should be noted that when Lignocaine (Xylocaine) is used a small area of analgesia does occur in the region of the anus. It is also important to remember that the technique should be abandoned if cerebrospinal fluid is tapped; failure to observe this rule has led to near catastrophes (Galley and Peel, 1944).

The use of the catheter technique is still held up in this country because of the fragility of the catheters available. The synthetic resins from which they are made are not nearly so tough as those used in the U.S.A. Our catheters tend to fracture in the region of the sacral hiatus where the mobility of the soft structures and the immobility of the sacrum produce most strain on the catheter (Bryce-Smith, 1950; Galley, 1950*a*). In the U.S.A. "nylon" catheters are used with an almost negligible incidence of fracture.

Drugs.—The drugs most used for sacral-extradural analgesia are as follows (Table I):—

TABLE I

Drug used	Onset in minutes	Duration in minutes
Procaine 1%	15–20	30–40
‡Metycaine 1·5%	10–15	30–45
Amethocaine 0·15%	20–30	90–120*
*Procaine 1% and Amethocaine 0·15%	10	90–120*
*†Lignocaine 0·75 to 1%	7–10	60–100
Cinchocaine 0·16%	15–20	70–120

*Hallett, 1953. †Cappe and Pallin, 1953. ‡Hingson and Edwards, 1942.

For some unexplained reason repeated doses of local analgesic solutions do not always reproduce their initial effect. This phenomenon is not usually noticeable until after several hours of caudal analgesia. If, therefore, prolonged analgesia is contemplated it is preferable to commence with, say, Metycaine and, should its effect fail after some hours of serial injections, to turn to a stronger drug such as Lignocaine. Lignocaine will often rescue a failing analgesia from some weaker drug but cannot, under similar circumstances, rescue itself.

The addition of hyaluronidase to analgesic solutions does not appear to affect the rapidity of onset of analgesia. Adrenaline in suitable dilution minimizes the risk of hæmorrhage in the extradural space and appears to increase the likelihood of stable analgesia. According to recent work this may be due not so much to vasoconstriction but to the fact that adrenaline and some similar sympathetic amines are local analgesics themselves (Wu, Harnagel, Brizzee and Smith, 1954).

Use in obstetrics.—Although continuous (serial) injection is the only method which gives complete relief of pain during labour it still suffers from the following disadvantages: the technique is difficult; the constant supervision is time-consuming; and the forceps-rate is increased. Reaction to these problems differs in the U.S.A. and the U.K. In the U.S.A. obstetric analgesia or sedation tends to be heavy and delivery by forceps after episiotomy is the rule rather than the exception. In the U.K. obstetric sedation is much lighter (to the point of being little more than nominal in some hands) and forceps deliveries are avoided unless strictly necessary. The general attitude to sacral-extradural analgesia in obstetrics has, therefore, been much the more conservative in the U.K. The present position is, therefore, as follows. Certain maternity hospitals in the U.S.A. are large enough to ensure that on many occasions there are several patients in labour at the same time. Caudal analgesia is induced in each patient by an anæsthetist or obstetrician-trainee seconded to the department of anæsthesia; but once analgesia is established a trained charge-nurse takes over and supervises the maintenance of analgesia. Every fifteen minutes the height of analgesia and the blood pressure is checked and charted. Should skin analgesia rise above the umbilicus or the systolic blood pressure fall below 100 mm. of mercury an anæsthetist or obstetrician is sent for, otherwise the nurse carries on by herself. In this country the indications for caudal analgesia are as follows: (*a*) to provide an "easy" labour for patients with pulmonary tuberculosis or morbus cordis; (*b*) for forceps delivery in the presence of fœtal distress; and (*c*) for emergency Cæsarean section on patients with full stomachs, e.g. prospective mothers suffering from diabetes. At one time it was thought that sacral-extradural analgesia was a specific antidote to spasm of the cervix uteri but several colleagues in other centres have informed me that they do not find this so (Galley and Peel, 1944; Galley, 1949).

Cæsarean section is as easily performed under sacral-extradural analgesia as with spinal analgesia and is slightly safer for two reasons: (*a*) there is no risk of meningitis and (*b*) the intercostal muscles are less affected. It is better than dorso-lumbar extradural analgesia because the pelvis is more thoroughly anæsthetized. In all forms of conduction analgesia, however, great care must be taken to prevent a dangerous fall of blood pressure before the baby is delivered. After delivery the retraction of the uterus greatly reduces the capacity of the vascular bed and the blood pressure suddenly rectifies itself. In other words, the uterus transfuses the rest of the body and restores the blood pressure previously lowered by sympathetic block.

Puerperal encephalopathy.—Sacral-extradural analgesia breaks the vicious circles of water retention and rising blood pressure associated with puerperal encephalopathy (Fig. 1). In addition, anæsthesia is sufficient for the delivery of the baby either by the natural passages or by Cæsarean section.

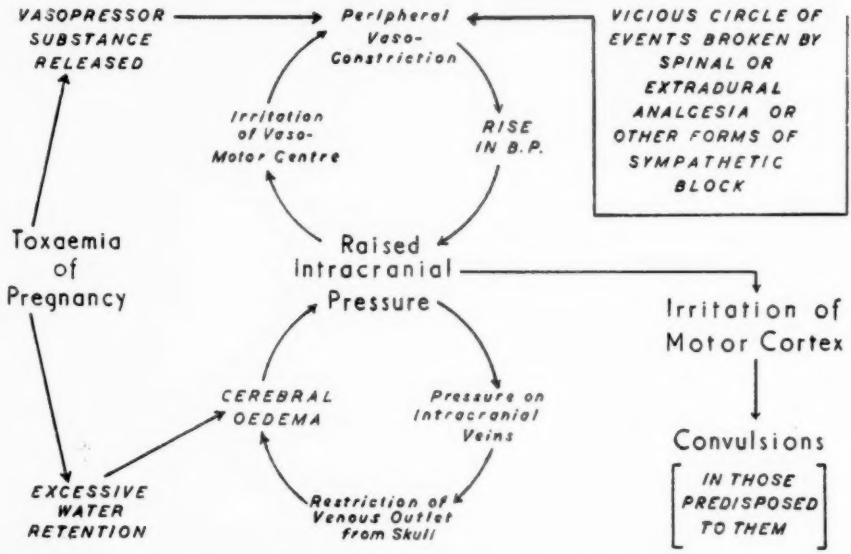

FIG. 1.—Vicious circles associated with puerperal encephalopathy. Schema—showing how the vicious circles of water retention and rising blood pressure interlock to produce puerperal encephalopathy. (Controversial causative factors of the production of a vasopressor substance have been omitted to avoid unnecessary complication.)

"*Non-rising*" *analgesia.*—Despite repeated doses of analgesic solutions it sometimes happens that analgesia fails to rise much above the level of the pelvis. This might be due to an abnormality in the anatomy of the extradural space, e.g. a "leaking" posterior wall to the sacrum, or to a hæmatoma separating the lumbar from the sacral-extradural space. In such cases successful analgesia—either for Cæsarean section or for vaginal delivery—can only be obtained by a combination of both types of extradural block. This is well illustrated by the following case which is of particular interest as the patient concerned was referred to King's College Hospital by Professor R. R. Macintosh.

Young woman in her early 30s who had had one normal delivery of a live baby two years before with almost continuous pain throughout a long labour.

She was admitted to K.C.H. in the early hours with regular but not very troublesome pains and was given: Potassium bromide, 30 grains; chloral hydrate, 30 grains.

11.30	Sacral-extradural analgesia prepared	Pains every 3 minutes and lasting for 2 minutes. Cervix: 2 fingers dilated
11.50	Metycaine 1½% 8 mil.	Blood ++ from needle. Needle readjusted until no blood appeared. No blood aspirated
12.00	Metycaine 1½% 32 mil.	
12.15		Analgesia around anus (more on right side). Contractions at 3 min. intervals. No more pain in back but pain in lower abdomen
12.30	Metycaine 1½% 20 mil.	Contractions every 2 to 3 min. Pain in groins only. Legs slightly heavy. "Pins and needles" in feet.
12.40		Contractions every 2 to 3 min. Still pain in groins but now going through to back. Very strong contractions
12.50	Lignocaine 1% 20 mil.	
13.05		Still pain in groins and upper back but much less intense and only felt at the height of the contractions

At this point it was decided to place a second needle into the extradural space, inserting it between the first and second lumbar spines as the extradural space is here fairly wide and still not too far from the nerve supply to the upper part of the uterus, i.e. D11 and 12. Analgesia then proceeded as follows:

Time	Sacral extradural injections	Lumbar extradural injections	Conduct of labour; efficiency of analgesia, &c.
13.10		Lignocaine 1% 2 mil.	2 to 3 min. intervals between contractions
13.20		Lignocaine 1% 5 mil.	Pain diminishing in back and groins
13.32	Lignocaine 1% 10 mil.	Lignocaine 1% 10 mil.	(Anæsthetist had lunch!)
13.48			Painless contractions at 3 min. intervals
14.10			Ditto. Analgesia to pin-prick to level of D11. Pin-prick felt only faintly in D10 area
14.35			Contractions beginning to be painful (abdomen and upper back)
14.40		Lignocaine 1% 10 mil.	Patient very sleepy
14.55			No pain in abdomen and upper back—pain returning in sacral area
15.00	Lignocaine 1% 10 mil.		Cervix ¾ dilated
15.17			Contractions painless again at 3 to 4 min. intervals
16.15	Lignocaine 1% 10 mil.	Lignocaine 1% 10 mil.	Anterior lip of cervix still palpable on P.V. examination
16.55			Patient asleep. Roused during examinations for fœtal heart rate. Cervix fully dilated
17.03	Lignocaine 1% 15 mil.		Needles removed. Patient prepared for forceps delivery
17.14			Forceps applied
17.17			Male child delivered. Breathed and cried within 30 seconds of delivery. No perineal tear
17.23			Placenta delivered—very little blood

This mother remembered very little of any pain after both types of extradural block had been induced—no doubt due to the sleepy state which supervened owing to the central effect of Lignocaine.

It is not suggested that this complicated type of analgesia should be encouraged but, after the patient's confidence had been built up in favour of conduction analgesia (and seeing that she had been referred by so eminent a colleague!) we felt that she could not be allowed to leave us in disappointment.

Use in surgery.—Although it is possible to use sacral-extradural analgesia for operations in the upper and mid-abdomen these are better served by dorso-lumbar extradural block; the exception to my mind is Cæsarean section because of the painful dragging on pelvic structures which renders the latter type of analgesia inadequate. Caudal analgesia is, therefore, mostly used for operations such as prostatectomy, cystoscopy and hæmorrhoidectomy as an alternative to low spinal analgesia.

Provided the usual precautions against a decline in blood pressure are observed it is astonishing how well elderly folk stand caudal as well as other types of conduction analgesia. Recently, at a demonstration organized by the South-West of England Society of Anæsthetists, I saw a low caudal analgesia given by Dr. T. R. Steen (Southfields Hospital, Bristol) to a frail and aged man for retropubic prostatectomy. The patient had chronic bronchitis and a very enlarged heart due to hypertension. A low caudal analgesia was induced with 12 mil. Lignocaine 1% and general anæsthesia effected with a small dose of thiopentone reinforced with nitrous oxide and oxygen. A bilateral rectus-sheath block was then given to minimize the intra-abdominal pressure which otherwise might have been transmitted via the bladder to the wound cavity and interfered with the surgical approach. After operation the patient soon awoke and was very fit indeed.

Therapeutic uses.—Certain types of *sciatica* respond to caudal injections. It is thought that the effect is mechanical and acts by creating sufficient pressure within the extradural canal to break down adhesions which may be distorting posterior roots of the spinal cord—indeed, similar effects have been achieved by using saline alone. This latter method, however, is painful and the use of a weak local analgesic (owing to the large volume injected), e.g. Lignocaine 0·5% not only makes the method painless but allows *gentle* manipulation of the spine to be conducted in order to augment the breaking-down of adhesions. *Low back pain* sometimes responds to similar treatment.

The sympathetic block which ensues from sacral-extradural analgesia is more convenient to give than multiple paravertebral blocks owing to the fact that only one needle has to be inserted. It may prove useful in the following conditions:

Vasospastic disease of the legs.—Not only is sacral-extradural analgesia useful as a diagnostic procedure, i.e. to ascertain the probable effect of sympathectomy, but it often improves the blood supply of the legs on its own accord. This is due to the fact that disease of the large vessels is often accompanied by spasm of the collaterals (Leriche, 1939); release of this spasm at a time when the blood supply is in a parlous state may make all the difference between life and death of a limb (Hingson, 1947, 1949; Steel, 1948; Galley, 1950*b*, 1952).

Caudal analgesia in common with other forms of sympathetic block has no action on the large vessels of the legs (Kinmonth, 1952) and is, therefore, useful as an anæsthetic for *embolectomy*. Not only does it produce the anæsthesia but it releases spasm in the collateral arteries and ensures a better blood supply to the limb.

If taken early, the *white-leg* of pregnancy or the puerperium readily responds to all forms of sympathetic block including caudal analgesia (Hingson, 1947, 1949; Steel, 1948; Galley, 1952).

We still use the method on people suffering from *cold feet*. The curious thing about these is how they all assure us that their symptoms are relieved although, at the time of injection, there was little or no rise in the skin temperature. Perhaps this is another indication that the blood supply to the deeper structures is independent of that of the overlying skin.

In all these cases injections may have to be repeated at intervals of a week until some measure of relief is achieved. If oily solutions are used one injection only may be sufficient (Galley, 1952).

Acute anuria.—This form of treatment is based upon the assumption that acute anuria is due to the reflex invocation of the renal "shunt", i.e. generalized spasm of the afferent arterioles supplying the functioning glomeruli of the renal cortex with a short-circuiting of the cortical blood supply via the juxtamedullary (primitive) glomeruli and the arteriovenous anastomoses of the arcuate-sponge structures in the juxtacortical area of the medulla (Trueta, Barclay, Franklin, Daniel and Prichard, 1947). Were this "shunt" really responsible for all types of acute anuria some form of sympathetic block (Bryce-Smith *et al.*, 1949) would be the obvious treatment but opinion is divided upon the subject and seems to be hardening against the use of extradural or spinal analgesia during the management of these unhappy cases. The greatest obstacle to the scientific assessment of such treatment is the fact that even without treatment some cases suddenly take a turn for the better after a few days.

Relief of pain of pelvic carcinoma.—Pain of this type can be relieved for varying periods by injecting 60 mil. of an oily solution of a local analgesic (e.g. Proctocaine) into the sacral canal (Kenny, 1947). Results are variable because of the differences in histological structure and physiological function of the two types of nerve associated with the conduction of pain (Galley, 1950*b*); also because of varying degrees of carcinomatous involvement of these nerves.

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Dr. P. R. Bromage, Chichester and Portsmouth Hospital Groups:

Indications for Lumbar and Thoracic Epidural Analgesia To-day

When a depot of analgesic solution, of the correct concentration, is placed in the epidural space a prolonged differential spinal block results. Within, the distribution of the block motor nerves are scarcely affected at all, while the smaller and less heavily myelinated sensory and sympathetic fibres are interrupted. This differential block produces three effects:

(1) *Analgesia* lasting between two and four and a half hours, according to the solutions used.

(2) *Reflex flaccidity in the segmental distribution of the block.*—Voluntary muscle tone depends upon an intact reflex arc. If the sensory component of the reflex arc is broken muscle tone is abolished, despite a functionally intact final common motor pathway to the muscle. Conversely, since the final common pathway is intact reflexes initiated at a higher level can still find expression in the analgesic

segments. For instance, *all* the spinal sensory nerves may be blocked, right up to the first cervical segment, and still respiration will remain unimpaired since the respiratory centre remains responsive to afferent impulses initiated by chemoreceptors, as well as the direct effect of blood carbon dioxide changes upon the centre itself.

Just as the intercostal motor nerves remain responsive to impulses from the respiratory centre, so also can they respond to afferent impulses arising from vagal stimulation in the upper abdomen. For example, firm traction on the stomach or duodenum may cause a motor response, resulting in the contraction of previously relaxed abdominal muscles, and possibly even a laryngeal spasm as well. Thus, an epidural block, however high, is not sufficient in itself for upper abdominal work—vagal reflexes must be damped down by additional measures.

(3) *Spinal autonomic nerves are interrupted* in the segmental distribution of the block.

A normal blood pressure is dependent upon an intact sympathetic outflow, therefore if sympathetic nerves are blocked the blood pressure will fall in proportion to the number of thoracic segments involved (Goepel, 1943; Bromage, 1951). This fall can be accepted, or corrected by vasopressor drugs, according to the degree of the fall, and the amount of hypotension required.

Extensive blockade of the spinal autonomic also results in interference with the heat-regulating mechanisms. Adrenaline secretion falls, the sweat-glands are paralysed, and vasodilatation occurs, so that the body tends to follow the temperature of its surroundings. In hot climates *hyper*pyrexia must be guarded against, and conversely, *hypo*thermia can be easily induced under cooler conditions.

An epidural block is, in effect, a long-lasting spinal analgesia with its teeth drawn. The dura is not punctured, so there is no contamination of the delicate subarachnoid structures, and no cerebro-spinal fluid is lost, so that dangers of meningitis, or ocular palsies or post-spinal headache do not exist, and the mechanics of respiration remain normal, even with a block up to the base of the skull. These conditions last for three and a half to four and a half hours when cinchocaine is used as the analgesic agent. If necessary, the block can be prolonged indefinitely by inserting a fine vinyl plastic catheter into the epidural space, so that intermittent injections can be given up the catheter. The lumbar route is obviously preferable to the caudal approach when an indwelling catheter is used, as there is less likelihood of soiling from the patients' excretions.

In Germany, viscous substances such as polyvinylpyrrolidone are added to the epidural solution, with the intention of localizing the block and prolonging its effect (Duttmann, 1943; Goepel, 1947). I have used polyvinylpyrrolidone in greater concentrations than recommended by the German workers, and yet have found no worthwhile difference from ordinary aqueous solutions, in either localization or duration.

The applications of the method are:

I.—Practical Indications

Surgical anæsthesia.—Despite glowing reports to the contrary, I do not believe that epidural block has more than a very occasional place in thoracic surgery. For thoracotomy absolute control of the lung is essential, and the intravenous relaxants combined with controlled respiration are undeniably the method of choice. For thoracoplasty, paravertebral block and local infiltration, with or without light general anæsthesia, give the best results and the driest field possible. To my mind it is neither justifiable nor possible to obtain the same degree of hæmostasis by a general lowering of the blood pressure in these cases. The patient is already ill from his disease, and may be reduced to the brink of anoxæmic anoxia by the surgical onslaught upon his thoracic cage—to add vascular hypotension to his sea of troubles may be a drop too much. In the rare case of an infected Sembs's space, and where it is felt there may be some contra-indication to general anæsthesia, an epidural block may be indicated; but if it is used, the blood pressure should be maintained at levels near normal by pressor drugs.

The most common application of the method lies in major surgery below the diaphragm, and the advantages will be discussed under the headings of Respiration, Blood Loss, Stress, and Post-operative Analgesia.

Respiration.—The intravenous relaxant and analgesic drugs provide excellent operating conditions, but at the price of respiratory depression. Under epidural block, on the other hand, tidal volume is well maintained, even in a steep Trendelenburg tilt.

In a number of cases complicated by emphysema and chronic bronchitis, the pattern of respiration was greatly improved after induction of the epidural block; a poor tidal exchange, with marked expiratory effort, changing to a free smooth rhythm, with increased excursions of the re-breathing bag. There are several possible explanations for this interesting phenomenon, but none of them are entirely satisfactory, and their discussion would be too lengthy to consider here.

Blood loss.—Hæmorrhage is markedly reduced by the vascular hypotension accompanying a high epidural block, and it is my impression that at any given level of blood pressure bleeding is less

with an epidural or subarachnoid block, than when the ganglion-blocking drugs are used. Table I shows a few representative cases.

TABLE I.—BLOOD LOSS DURING OPERATION (EPIDURAL BLOCK)

Sex	Age	Pre-operative blood pressure mm.Hg	Operation	Total blood loss in grammes
F	37	125/80	Total hysterectomy ..	200
F	83	200/100	Judet	90
F	80	200/110	Judet	45
M	78	210/120	Judet	150
F	44	150/90	Cholecystectomy	150
M	36	120/70	Partial gastrectomy ..	85
M	73	175/100	Retropubic prostatectomy	200

Operative stress.—Since there is much we still do not know about shock, I would prefer to avoid the word altogether, and speak of stress instead.

An attempt was made to assess the degree of adreno-cortical response to the stress of operation in three groups of patients undergoing abdominal operations. (1) A control group under general anæsthesia. (2) A second group, of lower abdominal operations under epidural block and light general anæsthesia; and (3) a third group of upper abdominal cases also under epidural block and light general anæsthesia. Blood samples for eosinophil counts were taken during induction of anæsthesia, and again one and a half and four and a half hours after the abdomen was opened.

The control group (Group 1) showed a typical fall of eosinophils starting after one hour, becoming maximal after four hours.

The lower abdominal cases showed an altogether different curve (Group 2). In these the afferent neural blockade was complete, and the eosinophil fall was delayed until after the block had worn off. The upper abdominals (Group 3) had an incomplete afferent blockade, since they must have suffered a certain amount of vagal stimulation, and these showed an eosinophil fall comparable with the control group.

Therefore, as far as the stress reaction is concerned, one can say that in *lower abdominal* operations the patient is shielded from stress until the operation is over, and he is back in bed. With upper abdominal cases afferent stimulation can occur despite the block, and the stress reaction is apparently unmodified.

There is no apparent virtue in postponing a normal adrenal cortical response to trauma in patients with an adequate adrenal reserve. But when acute or chronic cortical depletion has occurred, either through exhaustion or illness, or due to suppression of ACTH secretion by cortisone therapy (Salassa *et al.*, 1953), the presence of an afferent block may be life saving. By delaying further demands upon an already depleted cortex, time is gained to institute appropriate therapeutic measures, before cortical failure can occur.

Post-operative analgesia.—A single-dose epidural with 1·2% Xylocaine lasts about two to three hours, and with cinchocaine (Nupercaine) about three and a half to four and a half hours. Therefore, if Nupercaine is used, a two-hour operation will be followed by two hours of complete freedom from pain, when the patient can move about freely, and start his breathing exercises, with an almost normal vital capacity. He is thus able to start the post-operative period under the best possible conditions, and can clear his chest thoroughly before the onset of pain hampers his breathing and coughing.

II.—THERAPEUTIC INDICATIONS

Therapeutic blocks often need to be prolonged for some days, and so the continuous technique is usually indicated, with a catheter in the epidural space. When choosing between the caudal and spinal approaches one must decide which route is likely to be easier, most effective, and least likely to become soiled and infected. My own choice is for the spinal approach, for these reasons:

It is easier, particularly in fat patients.

It is likely to be more effective for any given dose, since the tip of the catheter comes into closer relation with the segments to be blocked.

It is less likely to become soiled and infected by the patient's excretions.

After insertion, the position of the catheter should be checked by X-rays, to ensure that it lies cleanly within the epidural space. 0·2 of a millilitre of radio-opaque solution is injected up the catheter, and lateral and antero-posterior radiographs are taken.

Therapeutic epidural block has its most dramatic effect in acutely painful conditions which are poorly relieved by other methods—for instance, acute pancreatitis, or the pain associated with dissecting aneurysm of the aorta. The methonium drugs have been advocated for the treatment of

both these conditions (Davies *et al.*, 1953; Pyke, 1953), but I have the impression that they afford only a partial relief of pain which is nothing like so intense as that obtained by an epidural block. Moreover, the ganglion-blocking drugs have uncomfortable side-effects when given in sufficient dosage. The patient develops a dry mouth and a considerable thirst, he cannot pass the time by reading because of blurred vision, and anything taken by mouth splashes about in a distended atonic stomach: any existing ileus, such as occurs in acute pancreatitis, is almost sure to be aggravated.

Needless to say, neither an epidural block, nor the methonium drugs should be given if there is the slightest doubt about the diagnosis—a patient with a perforated viscus is not likely to survive if treated by these methods alone.

Chronic disturbances of the vasomotor supply to the upper or lower limb, giving rise to pain or œdema, may be treated by continuous epidural block. For the upper limb the catheter may be inserted in a convenient space between the seventh cervical and third thoracic spines, and for the lower limb between any convenient lumbar spines.

Relief of hypertensive cardiac failure and diagnostic blocks are among the many other applications of this form of sympathetic blockade, in which it rivals the methonium drugs and is to be preferred to subarachnoid block. Conditions of the kidney and lower limb have already been covered by Dr. Galley, and so there is no need to repeat them now. It is merely necessary to point out that the lumbar route is available as an alternative to the caudal approach.

[For illustrations, *see* Bromage (1954).]

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Dr. W. W. Mushin drew attention to the great value of intrathecal alcohol to relieve pain due to carcinoma. He was regularly doing these injections for pelvic carcinomatosis and, in particular, for pain due to secondaries following amputation of the breast. He also pointed out that one of Dr. Galley's charts (not illustrated) showed that a patient having a caudal block was receiving anticoagulants. There was some danger of hæmatoma if an epidural or a paravertebral block was performed on such a patient. This happened sometimes when a sympathetic block was to be undertaken for the relief of acute embolism. Such a patient might have been put on anticoagulant therapy before the sympathetic block was contemplated.

One of Dr. Bromage's slides (not illustrated) demonstrated the extension of the epidural fat through the intervertebral foramen. This confirmed evidence published by Professor Macintosh and himself (1947). They had come to the conclusion then that the ease with which an epidural block was produced by a needle in the paravertebral region explained the remarkably high success rate of paravertebral block for abdominal surgery in years gone by. It was probably one or more successful epidural injections which were responsible for the successful block rather than the accuracy of up to, say, 18 separate nerve blocks.

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Dr. Massey Dawkins agreed with Dr. Thorne that the only remaining indication for spinal analgesia was that of an emergency forceps delivery of a woman in labour who had a full stomach. For caudal analgesia in labour he did not think Xylocaine should ever be used owing to its peculiar property of occasionally spreading much farther than was intended. In such a case the motor nerve supply of the uterus would be affected and labour would cease. Dr. Galley had asked for details of experience with Proctocaine. Procaine was the active principle of Proctocaine and it was a relatively weak analgesic. He had found that much better results were obtained by substituting Nupercaine for Procaine, the solution he used being the 5% oily Nupercaine, which had a similar formula to Proctocaine. With this solution he had obtained analgesia lasting for six months.

He did not agree with Dr. Bromage that epidural analgesia was very rarely indicated in thoracic surgery. For thoracoplasties he found it gave excellent results, and as there was only one needle prick, it was much less of an ordeal for the patient and much quicker. He would regard an epidural block as the anæsthetic of choice for radical excision of the breast, using a dose of 8–10 c.c. of 1·5% Xylocaine deposited between C7 and T1. With this small amount no fall of blood pressure occurred, the analgesia being almost entirely unilateral. Yet the field of operation was practically avascular, the mechanism of which was difficult to understand, as with a paralysed sympathetic nerve supply

the opposite result might be expected. Surgical comment on this method of anæsthesia for mastectomy had been most favourable. He would agree that a high epidural block was not contra-indicated in shocked and exsanguinated patients, provided that an adrenaline drip had been put up. But in case of sudden failure of a single drip it would be much safer if such cases always had two drips running before the operation commenced. If a further loss of blood occurred this must be replaced immediately, or there would be a disaster.

One of the great advantages of epidural analgesia was that post-operative breathing exercises could be started while the patient was still on the operating table, and, as a result, chest complications were infrequent. Also because of the prolonged analgesia, he had found that 14% of abdominal cases did not require any morphia at all after operation. As a result the incidence of distension and ileus was much less and convalescence more rapid. He would like to confirm Dr. Bromage's experience of the straying epidural catheter. One of his upper abdominal cases had excellent analgesia of the sacrum, but none in the upper abdomen. The remedy was, of course, to insert the Tuohy needle at the mid-point of the nerve supply to the field of operation and then to pass the catheter for a short distance only.

Dr. R. W. Cope said that the reference by Dr. Thorne to the recent hearing in the High Courts of Justice before Mr. Justice McNair was of everlasting importance to anæsthetists. The case referred to was that of Woolley and Roe *versus* Ministry of Health, Dr. Graham and Ciba Ltd. In that action two distinguished and senior neurologists gave it as their firm opinion that cauda equina lesions and spinal arachnoiditis following the injection of a spinal anæsthetic drug were often due to the unexplained action of the drug itself upon a particular patient. This opinion was contested most vigorously by anæsthetists called both for the plaintiffs and for the defendants. It would be remembered that the President of the Section, Professor R. R. Macintosh, was one of those anæsthetists who thought that there was stronger evidence for other causes of permanent paralysis than incrimination of the drug used, and it was therefore a wonderful experience to listen throughout the hearing of a long day in the Court to the careful and most dignified explanations put forward so quitely, and yet so wisely, by their President. In a reserved judgment the learned Judge made it clear that he accepted completely the evidence of the three anæsthetists called before him in preference to the explanations given by the neurologists and a consultant surgeon.

One further point on another subject was made during this judgment, namely, that an anæsthetist reaching the rank of consultant status was entirely responsible for his own actions, and he could not shelter behind the authority of any other consultant person in the theatre or the Board of Management of his particular hospital.

Since this action was the subject of an Appeal against the judgment it was impossible to comment further on the details of this interesting case.

Dr. H. R. Youngman remarked that they had been using continuous extradural analgesia in selected obstetric cases for four years at Cambridge, and had continued to find it very safe and useful. In cases of dystocia they had no real proof that it hastened dilatation; but all the same it was most valuable in these long labours, preventing exhaustion of the mother without harming the child. Occasionally in a long case they found that refills were required more and more frequently until in the end the necessary level of analgesia could not be maintained without toxic symptoms developing.

The President said that one striking feature of the recent legal cases in London was that distinguished neurologists and neurosurgeons to whom cauda equina lesions had been referred, had not communicated with the anæsthetist concerned so that they had no information on such important details as methods of treatment of the ampoules and syringes used, or of the experience of the anæsthetist himself. They just inferred that the tragedy lay in some inherent idiosyncrasy of the patients to the local anæsthetic used, despite the fact that one of them had previously had a spinal anæsthetic without ill-effect. When a tragedy in any way comparable followed the administration of a general anæsthetic, the first things on which information was sought were the experience of the anæsthetist and details of technique. He did not believe a patient had any more tendency to develop paralysis after spinal analgesia than he had to die after, say, Pentothal—provided the anæsthetist displayed the care patients were entitled to expect.

JOINT MEETING No. 2

Section of the History of Medicine with Section of Odontology

Chairman—ARTHUR BULLEID, F.D.S., L.R.C.P., M.R.C.S.
(President of the Section of Odontology)

[*February* 3, 1954]

C. E. WALLIS MEMORIAL LECTURE, 1954
[Number 5]

Dental Operations Practised in Primitive Communities

By Professor HUMPHREY HUMPHREYS, O.B.E., M.C., M.B., Ch.B., M.D.S., F.D.S., F.S.A.

I MUST be one of the few people present to whom C. E. Wallis, in whose memory this lecture was founded, was known personally. Besides being interested in dental history he was the principal pioneer of school dentistry in this country and I well remember his telling me this story nearly fifty years ago. The bilateral extraction of molar teeth in children was about the commonest operation he was called upon to perform. The injection of local anæsthetics had not then been introduced into dentistry, general anæsthetics were not normally available in schools, so he trained himself to extract two molars simultaneously, one with each hand, while an assistant held the patient's head. This hurt the child once instead of twice; but by the standards of to-day it seems a primitive procedure and it was the recollection of this tale that influenced me in the choice of my subject.

The student of anthropology is presented with this paradox. Though many of the routine operations of dental surgery have been practised some time or somewhere in the world by primitive communities, they are commonly carried out not for therapeutic purposes but for reasons of ritual or cosmetic considerations. The commonest operation of all is the extraction of front teeth but it is seldom, if ever, performed on account of caries. Dental caries is as old as *homo sapiens*—even older for it is found not only in his predecessor Neanderthal man but in 2% of wild monkeys. But with uncivilized peoples, ancient or modern, or in other animal species it rarely affects the front teeth and mainly attacks the premolars and molars. In the great majority of cases primitive tooth extraction is performed on the incisor teeth as one of the initiation ceremonies performed at puberty. But before the motives or the methods of the operation are described, its distribution in time and place calls for consideration. It would appear that this curious ritual goes back to the last Ice Age, to the time when man was still a primitive food gatherer and had not yet taken the decisive step of subjecting Nature to the processes of food production. It was practised by the troglodyte Natufians of Mount Carmel who have been dated early in the Mesolithic period, and by some of the late Palæolithic Capsians of North Africa, but it was never a universal custom. In space it is in the main confined to Africa south of the Sahara, Australia and the Pacific islands including Tasmania, the East Indies and the Philippines. I have been unable to find records of its regular observance by the indigenous races, white, yellow or brown, of Europe, Asia and the American continents, with the exception of some aboriginal tribes in Indo-China allied physically to the Australoid stock. The Natufians of Palestine and the Capsians are only partial exceptions for Palestine is part of the land bridge which connects Asia with Africa, and in the last Ice Age the Sahara was not the impenetrable desert that it is to-day: large parts of it were grassland which could easily be traversed thus allowing southern customs to penetrate to the Mediterranean.

This distribution for the custom of incisor extraction suggests some association with the negro race. The extinct Tasmanians were negroid, the natives of Papua and Melanesia belong to the negrito or Pacific branch of the negro stock. The Australian aborigines, it is true, are not negroid but all the evidence suggests that they received the elements of their culture from many sources and may well have acquired this custom from their neighbours to the South, or North, the Tasmanians or the natives of New Guinea. The latter may also have transmitted it to other Pacific Islands. In the great majority of cases to-day it is carried out on boys and girls about 12 years of age, the usual age for the onset of puberty; there is no general uniformity in the selection of teeth. With Tasmanians and Australians one or both of the upper central incisors were sacrificed and this was the commonest choice of the primitive Bushmen of South Africa and the tribes of the African equatorial belt. But

with a number of Kaffir communities two or four lower incisors were selected and sometimes the lower canine teeth were included. This was the case with the Bangoro tribe of Uganda. As with most primitive customs it is not possible to give a clear account of the underlying motives for this ritual. It is sufficient for the boys and girls who undergo it that it is a universal fashion and that if they evade it they will always be conspicuous and a butt for the ridicule of the majority. When we witness the much more expensive and perhaps equally exhausting ordeals to which modern women subject themselves so that their hair, their eyebrows or their finger-nails may be changed from their natural colours and forms to those demanded by the fashion of the day we can readily understand the tyranny of custom over the small societies of primitive man. Nevertheless we can perhaps divine something of the motives which led to the adoption of this painful and—to our eyes—disfiguring rite.

The idea of sacrifice is as old as human thought. In Christian countries everyone, however ignorant of anthropology, has heard the story of Abraham's intention to sacrifice Isaac, his beloved and only-begotten son, as a propitiatory offering to his God. Similar stories figure in the myths of many nations and readers of Sir James Fraser's "Golden Bough" will find plentiful examples. Indeed a sacrifice similar to Abraham's is in a certain sense the basis of the Christian creed. But the idea of substituting for a human life that of an animal is also extremely ancient; and perhaps older still is the sacrifice of a portion of the human body. Circumcision is a widespread custom in primitive society, and we have evidence that amputation of the terminal phalanx of a finger, practised till quite recently by the bushmen of South Africa, was performed in the earliest human societies of which we have any record, the Upper Palæolithic hunters of Europe. The evidence lies in their art, those cave paintings so miraculously preserved. A common figure both in Aurignacian art—the earliest of all—and in that of their successors, the Magdalenians, is the outline of a human hand on the cavern wall and in a number of these we can see fingers with the terminal phalanx missing. It is highly probable that the ritual of tooth extraction owes its origin to this same idea of sacrifice. Finger amputation and circumcision, like baptism, are usually performed on infants. That is not possible for tooth extraction since the permanent incisors do not erupt till the seventh or eighth year and perhaps that is why the operation is reserved for the initiation ceremonies of puberty. Nevertheless it is recorded of the Masai in East Africa that they make doubly sure by extracting the upper central incisors twice, the milk ones when they erupt (about the age of 8 months) and the permanent ones at 12 years.

Though there can be little doubt that the idea of propitiatory sacrifice is central, other subsidiary motives for tooth extraction are sometimes adduced. It is, however, probable that some of these were invented to satisfy the curiosity of inquisitive Europeans. James Chapman recorded in 1868 that the Damara remove the four lower incisors to make them lisp since their dialect, like Castilian Spanish, demanded lisping for perfect pronunciation. The Masai, who removed the upper centrals, claimed that this enables them to feed patients afflicted with lock-jaw, a common disease with them. The Arunta tribe of Australia removed the central incisors of boys and girls before marriage to produce a resemblance to "Alailinga", a peculiar small dark cloud with a light margin said to portend rain. The Oyakumbi of Central Africa had the lower central incisors removed and the upper ones filed (*see later*) with the exception of members of the royal family who kept their teeth intact. The operation on their subjects was said to stamp them as the cattle of their rulers since cattle have no incisors in one jaw.

The operative procedure varies. The commonest both with the Australian and African tribes is for the patient to lie on the back with his or her head between the knees or on the lap of the squatting surgeon. The latter places one end of a stick (or in modern times a metal rod) against the tooth and taps the other end sharply with a stone. Sometimes a single heavy blow will knock the tooth out though there is a risk of fracture. To avoid this some tribal dentists loosen the teeth with a series of milder blows and then extract it with the fingers, Nature's forceps. But the use of an elevator is not unknown. In the Bakitara tribe of Central Africa boys and girls lose the six lower front teeth at puberty. They sit between the legs of the dentist's assistant who holds their arms and legs with his own, while the surgeon levers out the teeth one by one with a pointed peg of iron 6 in. long, which he drives down between the gum and the tooth. Amongst the Lango of Uganda the two lower central incisors are removed in a similar manner, whilst in some Kaffir tribes the final removal after the tooth is thus loosened is performed with the fingers.

The more difficult operation of removing a molar tooth is sometimes performed not as a religious rite but for the relief of pain. Pain may arise from a carious cavity, from an abscess at the root-end, or, amongst primitive people, not uncommonly from exposure of the pulp by severe attrition due to the gritty nature of the food. Any collection of skulls of modern savages or from Anglo-Saxon graves will show examples of this. Extraction in such cases is usually effected by first loosening the tooth with a stick tapped repeatedly by a stone mallet, as in the extraction of incisors just described. This process may have to be repeated on several days till the tooth is loose enough to be removed by strong fingers. Sometimes if the tooth is sufficiently separated from its neighbours—by caries or otherwise—a sinew may be twisted round the tooth with the other end round a strong stick which is levered against the jaw till the tooth is dragged out. Such procedures, employed to-day by Kaffirs, must be ancient. In 1937 I examined the bones excavated from the Pre-Roman Iron Age Camp

on Fredon Hill. In one lower jaw a second molar had been successfully removed, presumably by one of these methods; the bony socket had healed and the other teeth were healthy.

In ritual extraction the tooth is usually flung away as far as possible immediately after removal but amongst the northern tribes of Central Australia, where every activity is dominated by magic, its disposal is less simple. Sometimes it is powdered and eaten—by the mother in the case of girls, by the mother-in-law in the case of boys. In other tribes it is buried by a water-hole in the belief that it will check the tropical rains. Similar superstitions survived until quite recently even in Europe where the disposal of a milk tooth lost by the natural process was considered to be of considerable importance by old-fashioned nursemaids.

Another class of dental operation widely practised amongst primitive people consists in altering the shape of the front teeth by some form of mutilation. It is combined with ritual removal of other teeth by some Kaffir tribes and by aboriginal tribes of Indo-China and the Pacific Islands: but it also flourished in the past amongst the pre-Columbian peoples of Central America, who did *not* practise dental extraction. It is not recorded of Tasmanian and Australian aborigines. Perhaps the simplest mutilation was that of grinding down the teeth with stone till a space appeared between the upper and lower incisor edges. This is common among the aborigines of Indo-China and often causes exposure and subsequent death of the tooth pulp with resulting infection. Indeed these results follow most of the mutilations performed on children. Sometimes modern tools are borrowed for the purpose. In the 1951–52 volume of *Man* there is an article by a missionary,[1] illustrated by photographs, which describes how the upper incisor and canine teeth of a girl of 12 belonging to the Raday tribe of Indo-China were sawn off at the neck by a native operator equipped with a European hack-saw. The operation took an hour and a half and the girl lay perfectly still showing no sign of pain.

Another mutilation common among Kaffir tribes in the Philippines, and formerly in Central America, is that of shaping the incisors to a point. This is done either by chipping away the corners of their flat incisal edges by a chisel and mallet or by grinding with a stone. In Central America it was not uncommon for the incisal edge to be divided by two or three vertical grooves to resemble the teeth of a comb. Most of these mutilations are performed as part of the initiation ceremonies of puberty and it is probable that they are nothing more than fashions. Fashions amongst primitive people are less fleeting than with ourselves. But a magical significance may attach to some of them. It has been claimed, for example, that in some tribes they recall cannibal habits of the past by imitating in man the dental aspect of the carnivorous beasts of prey.

The appearance of the teeth is sometimes changed without alteration of their shape by coating them with some artificial application. Some tribes in New Guinea and the Philippine Islands cover their teeth with a black lacquer prepared by mixing a soil containing sulphur with a pungent leaf: they have to abstain from eating or talking for several days while the lacquer hardens. Marco Polo records that in the thirteenth century wealthy Chinese sometimes covered their teeth with thin plates of gold, an anticipation of jacket crowns. But the most interesting operation in this class is that practised by the pre-Columbian peoples of central America, who succeeded in inlaying artificially prepared cavities in their front teeth with precious stones. This astonishing achievement deserves a fuller description. Its first practitioners were the Maya of Guatemala and Yucatan in central America. During the centuries which in Europe saw the Roman Empire declining into the Dark Ages, they evolved the earliest form of civilization to flower in the New World. They were clearly very tooth-conscious, for though they never appear to have practised ritual extraction, they were much addicted to the mutilation of their upper front teeth along the lines just described. And in addition they sometimes drilled small circular holes in the visible surface of the front teeth and inserted therein accurately fitting circular inlays of precious stones. In the great majority of cases these were green—jade, jadeite or turquoise—though rock crystal and obsidian have been recorded. The Maya passed on this art to the Mexican civilization which succeeded their own, and it has been occasionally recorded elsewhere though never with the remarkably accurate technique observed in the jaws exhumed from pre-Columbian graves in central America. For example, crude inlays of jewels in the front teeth were to be observed fifty years ago amongst the head-hunters of Mindanao in the Philippines.

The art was imitated by the neighbours of the Maya to the South as well as in Mexico, for it has been recorded from Ecuador where in one case the inlay was of gold. But it was never practised by the Peruvians, who were experts in the operation of trephining the skull. It may have been, like the mutilations, merely a matter of fashion but the preference for green stone suggests an ingredient of magic. Green is the colour of most vegetable life and it is recorded that the Mexicans used jade for money. Our knowledge of the technique is derived from the examination of skulls and these show that the cavities went down to the dentine and their preparation, which must have been effected by pointed stones rotated by a simple bow drill, was often followed by death of the tooth pulp and subsequent abscess at the root-ends. The inlays were held in by some sort of cement but its nature has never been determined. It was probably organic in character of animal or vegetable origin but analysis shows that silica was an ingredient.

[1] SMITH, G. H. (1951) *Man*, **51**, 33.

It is obvious that all the operations hitherto described must have been painful and it is often claimed that they originated as tests of endurance. This is doubtful for it must be borne in mind that people leading a primitive existence are far less conscious of pain than those enjoying the comforts of civilization. I have some personal experience of this for during the First World War I served with a cavalry division in the Sinai Desert, Palestine and Arabia. When campaigning we slept on the ground under the stars, or not infrequently in our saddles on a night march. We seldom washed, changed our clothes or had our boots off and most of us became quite insensitive to any discomfort short of severe wounds. I served as a medical officer in a field ambulance but in view of my dental qualification, the regimental medical officers frequently referred to me difficult tooth extractions or cases in which they had broken off the crowns in an unsuccessful attempt. I was not provided with any anæsthetic, local or general, but it was a common experience after I had extracted a difficult tooth for the patient to ask me to extract a few more that had troubled him "while I was about it". None of them ever showed signs of feeling pain. This experience relates to the first half of the war before the Army was provided with professional dental services.

Primitive peoples suffer from other dental diseases besides caries, the commonest being chronic inflammation of the tooth-supporting tissues with progressive loosening of the teeth. Indeed it has often been remarked that races with whom caries is relatively rare are more prone than modern European communities to this type of disease. Certainly it is far more common than caries amongst Indians and Africans. A primitive method of preserving loose incisors is to twist gold wire around them and then round the stronger-rooted canine teeth so that the latter will support their weaker neighbours. This idea occurred independently to two widely separated peoples, in South America and Italy. At Esmeraldas in Ecuador a pre-Columbian tomb has yielded jaws with the teeth splinted in this fashion and the Etruscans of Italy invented the same technique at least as early as the seventh century B.C. This community migrated from Asia Minor early in the last millenium B.C. and introduced new arts to Northern Italy. Having hit on this idea of splinting loose teeth the Etruscans rapidly improved on it. The gold wire was replaced by gold strips fitted to the loose incisors and to the canines. If, in spite of the splinting, any of the incisors became hopelessly loose or were lost they were replaced by substitutes, the earliest examples of bridgework in history. Most commonly it was the crowns of human incisor teeth which served as substitutes but in Coreto Museum there is a jaw in which the incisor of an ox has been carved to represent and replace two human teeth. In a museum at Florence there is an example of Etruscan bridgework in which a gold crown cast by the *cire perdu* technique replaces a human tooth, an astonishing anticipation of modern methods. The replacement of lost premolars and the use of premolars and molars as bridge-abutments were achieved in due course by the Etruscans and their Roman pupils. This gold bridgework was skilfully soldered and its accurate adaptation proves that good impressions of the mouth were obtained. The Etruscans were great traders: many of the numerous sixth century B.C. Greek vases in the British Museum were exhumed last century from Etruscan tombs and these people taught their technique of dental bridgework not only to their neighbours and successors, the Romans, but to the Greeks and Phœnicians. The earliest code of Roman law, that of the fifth century B.C. Twelve Tables, after forbidding the burial of gold in tombs makes an exception of gold fitted in the mouth for purposes of prosthesis. The remarks in the Satires of Horace and the Epigrams of Martial on ladies whose teeth were not their own refer to this form of bridgework learnt from the Etruscans. But this theme is leading us too far from our proper subject of primitive dentistry.

The oldest existing work on surgery is the Smith papyrus, now in the Brooklyn Museum. The manuscript was written in the seventeenth century B.C. near the beginning of the New Empire but it was considered by Breasted, who published a translation in 1930, that it is a copy of a text compiled a millenium before in the days of the Old Empire. It contains no description of purely dental techniques but it does describe an operation often performed by dentists, that of reducing a dislocation of the lower jaw at the temporo-mandibular joint. It is remarkable that the method recommended nearly 5,000 years ago is exactly the same as the one we employ to-day.

The complete excavation of a carious cavity and the subsequent insertion of a permanent filling has, of course, only been made possible by modern equipment, but primitive people sometimes deal, and deal successfully, with the pain of an exposed pulp. Australian aborigines will heat the pointed end of a stick in the fire and thrust it into the cavity. The Moros of Liberia fill it with country salt (potassium hydroxide) or red pepper seeds, either of which, like arsenic, produces death of the pulp and stops the pain. Many savages employ toothpicks, or brush their teeth with green sticks frayed at the end. This is still the standard toothbrush in India, a very efficient one which I have myself used on active service when removed from the resources of civilization. To-day with increasing European contact most of the operations I have described are becoming obsolescent.

NOTE.—It would be tedious to detail all the numerous works on Anthropology from which the facts mentioned in this paper have been culled. Spencer and Gillen's works on the Australian aborigines are standard, Fraser's "Anthologia Anthropologica" contains much curious information, and Weinberger's "Introduction to the History of Dentistry" is a mine of information. There is a good account of pre-Columbian dental practices by Borbolla in the *American Journal of Physical Anthropology* 1940.

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Anticoagulants in Coronary Occlusion

By A. RAE GILCHRIST, M.D., F.R.C.P.

THE keynote of anticoagulant therapy is prophylaxis—a fact which makes the clinical evaluation of these drugs much more difficult than the assessment of a remedy employed solely for its curative properties. Anticoagulants are used in clinical work mostly with three objectives: (*a*) for the prevention of thrombus formation, (*b*) for the prevention of an extension of a pre-existing clot, and (*c*) for the promotion of its dissolution and organization.

In a variety of well-defined post-operative conditions these objectives can usually be achieved. Myocardial infarction, however, is a disease of extremes and subject to wide variations: the acute infarct may be fatal within minutes, or it may be silent or so trivial as to escape recognition. The illness does not readily conform to a strict pattern and hence deductions regarding the efficacy of any particular agent designed to modify its course are naturally difficult. The intermediate groups of moderate severity are commonly encountered in hospital practice, and give rise to much uncertainty. For the individual patient complications are largely unpredictable, both in time and in site. Prognosis is influenced by a number of variables, and, furthermore, the character and severity of the disease varies. The mortality rate after a coronary thrombosis is highest in the first few days of the illness, and therefore the longer the delay in securing hospital accommodation, the lower the death-rate for that particular hospital group. Practice varies in different localities and to compare mortality rates for hospitals where conditions are not exactly similar is apt to be fallacious. Present-day knowledge of the action and use of anticoagulants is far from complete.

Our original experience (Tulloch and Gilchrist, 1950) was based on two simultaneous control and treated groups of patients admitted in purely random fashion to two adjoining hospital pavilions, without any attempt at selection. After close analysis we concluded that our two samples were sufficiently homogeneous in respect of age, sex, severity and duration of the illness, to warrant comparison, to justify preliminary conclusions and to encourage a continuation of the investigations. Having now observed 434 consecutive patients, we have not, so far, found it necessary to modify our main conclusions.

Dicoumarol was first employed, later Tromexan (Tulloch and Gilchrist, 1951), and it now appears that Dindevan (phenylindanedione) has many advantages. Treatment is commenced with heparin, 20,000 units intramuscularly at 8-hourly intervals. This is continued for twenty-four to forty-eight hours, by which time the oral anticoagulant also commenced at the time of the patient's admission to hospital is usually influencing the prothrombin time. In our laboratory the prothrombin times are estimated each morning and the dose of the oral preparation regulated accordingly. Anticoagulants are employed for the first four weeks of the illness, when thrombo-embolic complications are most commonly experienced.

The mortality rate for the control series is 42·2%, as compared with 19·5% for those receiving anticoagulants. Our experience confirms the view that the prophylactic use of these drugs is capable of reducing the death-rate by half during the first six weeks of hospital care following the onset of the acute attack. Similarly, thrombo-embolic complications can be reduced from 26% to 10% over the same period, and deaths directly attributable to this cause reach minimal proportions. These findings are in keeping with the latest experience of Wright, Beck and Marple (1954).

It is sometimes argued that anticoagulants are unnecessary for the mildest attacks of myocardial infarction because 60% of hospital patients survive their six weeks' stay in hospital and many make good and lasting recoveries without the use of these drugs. This attitude takes little account of the needs of the individual patient, whose immediate future is so often treacherous even after a minor attack. Which one of us is so endowed with prophetic powers as to select on the first day of the illness the patient who will make an uncomplicated recovery? All of us have seen patients, mildly affected at the onset, who within a few days have had a major recurrence or experienced some other catastrophe. To delay the use of anticoagulants until a thrombo-embolic complication has occurred is to deny the therapeutic objectives and to court disaster.

Anticoagulants must be used as soon as the diagnosis is established and the severest cases transferred to hospital at the earliest opportunity. It is the badly shocked and gravely ill patient who stands to gain most benefit from this particular course of treatment. Our experience is that without the help

of anticoagulants 80% of patients showing a moderate to severe grade of cardiogenic shock d within six weeks of the onset. Left at home, often with inadequate nursing care, deprived constant supervision, and often perforce with makeshift arrangements for treatment during th first critical twenty-four or forty-eight hours, these patients often face greater risks than those entailed by their immediate transfer to hospital. Again, local conditions must influence the decision which the practitioner must make in difficult circumstances. The prompt use of heparin should be encouraged even before the patient leaves home.

Just as the exact mechanism of blood clotting remains in doubt, so also the scope of the action of the anticoagulants at present in use has yet to be decided. It is true that our expanding knowledge of pharmacological action depends in large part on specialized techniques of investigation not hitherto available and on increasingly refined methods of observation and measurement. Although anticoagulants can be regulated reasonably well for clinical purposes by prothrombin-time estimations, the range of their activity is not necessarily restricted to this particular function. Indeed, there is evidence to suggest that in the reduction of the mortality of the first six weeks anticoagulants may play a part in lessening the evils of the severer grades of cardiogenic shock (Gilchrist, 1952). At all events the reduction in the mortality rate observed in the treated series of patients is not entirely explicable on a decreased incidence of frank thrombo-embolic episodes. It is unreasonable to decry the use of a drug because its actions in man are imperfectly understood.

No one can safely employ these drugs without reliable laboratory control. The one danger is hæmorrhage. Broadly speaking, it arises as a result of (*a*) internal factors peculiar to the patient, in particular ulceration in the alimentary tract, and serious hepatic or renal disease, or (*b*) external factors concerning local conditions, in particular an inability on the part of the doctor to ensure reliable laboratory control from day to day. With increasing experience in the handling of these patients, and in regulating the dose of the oral preparation as determined by strict laboratory control, difficulties are seldom encountered. In our series hæmorrhage has only been noted in 11% of the treated group. In 2 patients, observed early in the series, bleeding undoubtedly contributed to death. Hæmaturia, epistaxis, or hæmoptysis occasionally occurs in a mild form and soon subsides when the anticoagulant is reduced or discontinued for a day or two. If the prothrombin time is unduly prolonged, it is usually recommended to employ water-soluble vitamin K in a dose of 60 mg. or more intravenously when hæmorrhage occurs, but we have seldom found it necessary.

Conclusions

Anticoagulants make a contribution to the prevention of unpredictable catastrophes in a disease characterized by much uncertainty and by a high mortality rate in the first six weeks of hospital treatment. They are not an infallible remedy but their employment is justified by a halving of the death-rate and by an even greater reduction in thrombo-embolic episodes.

With reliable laboratory control for the day-to-day regulation of the dosage of these drugs, serious hæmorrhage is seldom encountered and no harm results from their use.

The employment of anticoagulants has widened our outlook on the problems of acute myocardial infarction and has revealed our therapeutic shortcomings. There is still much to learn regarding the immediate effects of these drugs and their long-term influence.

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Anticoagulant Therapy in Coronary Occlusion

By William Evans, M.D., D.Sc., F.R.C.P.

Before turning to deal directly with anticoagulant treatment in coronary occlusion, there is a need to define conditions that should govern the acceptance by the profession of a particular medicine as orthodox in the treatment of any ailment. That a patient should have faith in medicine is an admirable thing; it helps him to get well. A doctor's faith in a remedy, however, should be founded on premises other than a simple hope that it will do good, and on a reliance gained from a clinical trial scientifically controlled. Even if we admit the influence of fashion on therapeutics we must never change a form of treatment just because it is fashionable to change.

It is better for a new remedy to be received with a quiet scepticism than with a boundless enthusiasm, because a wiser judgment on its real and lasting benefit is more likely to follow. There are many reasons why a new remedy is hailed with undue enthusiasm. Among them are the desperate need to alleviate or cure some fell disease, the demonstration of a specific effect in the experimental animal, the compelling advertisement which appears to brook no contradiction, its warm recommendation by a medical colleague, based too often on a limited experience, its acceptance by another country politically in the ascendency, the truism that it is always the latest song that an audience applauds the most—a sentiment born on the lips of Horace—and the demands made by either patient or relative. There is evidence that we are losing our self-reliance and that we yield too easily to the whims and fancies of our times and our patients. One of the main functions of a doctor is to manage his patients, and when the patients manage their doctors, and there are ominous

signs that this is taking place, medicine will have surrendered its professed scientific equipment for its ancient cloak of quackery. There is more danger in this than most appear to be aware of; thus, we find it recorded that 50% of American physicians using anticoagulants admitted that they did this because they were pressed to do so by their patients. Progressive medicine should provide that every new remedy must be submitted to a Therapeutic Trials Tribunal before it is dispensed to patients or included in the British Pharmacopœia. Such a body would outline a plan for an investigation to test the therapeutic value of the drug, and allocate the problem to those competent to solve it, and with facilities to carry out the work and at several centres. A model of such an investigation is afforded by the Christie Report on penicillin in the treatment of bacterial endocarditis. Before a new and potent remedy is accepted for general use it should satisfy a *Code of Efficiency* and such a code should demand three requirements of each drug: First, that it should produce noticeable improvement in the majority of patients where its trial has been justified. Secondly, that such improvement should never be less, and, in the large majority of patients, should be much greater than that produced by a placebo. Thirdly, that the remedy can be dispensed in a convenient form and without risk of producing injurious effects in the patients.

The Incidence of Coronary Thrombosis

Obviously the object of the treatment is to prevent clotting and primarily to prevent thrombosis within the coronary circulation, so that it is first necessary to examine the incidence of this event as a forerunner of, an associated finding in, or as a sequel to, cardiac infarction. There are a number of observations on this. In eight such investigations (Table I) an absence of clotting in the coronary arteries was found in some 20% to 90% of cases examined at necropsy with an average of 57% for the whole series. This means that had anticoagulant therapy been a universal procedure in these cases with cardiac pain it would have been given to prevent clotting which certainly never took place in 1,358 among 2,351 patients. Thus, anticoagulants dispensed with the purpose of preventing coronary thrombosis can do no good in more than one-half of all cases of cardiac infarction, while in each it can do harm. It is a good precept that no patient should be the worse for seeing a doctor; the patients I have just cited might have been the worse for seeing some doctors.

Table I.—Incidence of Thrombosis within the Coronary Circulation in Cases of Cardiac Infarction Examined at Necropsy

Authority	Number of cases	Coronary thrombosis present	Coronary thrombosis absent	
			No.	%
Nathanson (1925)	113	24	89	78
Lisa and Rirg (1932)	100	24	76	76
Appelbaum and Nicholson (1935)..	150	78	72	48
Wright-Smith (1936)	495	45	450	90
Bean (1938)	300	240	60	20
Gross and Sternberg (1939) ..	153	116	37	24
Meesen (1944)	590	237	353	60
Yater *et al.* (1948)	450	229	221	50
	2,351	993	1,358	57

Since anticoagulant therapy cannot reduce the mortality rate by lessening the incidence of coronary thrombosis in more than one-half the cases, does it in fact reduce it in the other half destined to develop thrombosis? It is not difficult to test the curative value of a medicine in a disease which invariably terminates fatally in the absence of a specific remedy as in the case of bacterial endocarditis. In an illness where recovery takes place without any remedial help, the claim of a particular form of treatment should be rigidly tested lest the credit of spontaneous recovery be erroneously allotted to the therapy that happens to be administered at the time. It is necessary, therefore, in the case of cardiac infarction, not only to compare the effects of an active medicine with a placebo, but also to ensure as far as is possible that special influences are operating to the same degree in both test and control series. Thus, the factors which are known to affect prognosis must be taken into account, and among these are the size of the occluded artery, the place of the infarct, the state of the adjoining collateral circulation, the age of the patient, and the presence of heart failure.

Mortality Rate in Cardiac Infarction

When the mortality rate in cases of cardiac infarction treated with anticoagulants and with more orthodox measures is examined (Table II) it is not clear why such comparison should have led so many to favour anticoagulant therapy for this has been done on insufficient evidence. Thus, we have a most ardent protagonist of this treatment (Wright *et al.*, 1948) claiming for it a mortality rate of 15% against 24% in the control group, and five years later (Wright, 1953) a mortality rate of 7% against 13%. Since it is impossible to predict in a patient with cardiac pain that the course of the illness is to be a favourable one, surely a different interpretation may be given to these results, namely, that a mortality rate of 15% during anticoagulant therapy compared unfavourably with one of 13% in a control group. Rytand (1951) quotes another instance where a different interpretation might be given to the published results; it concerns a report where a mortality rate of 40% among patients with cardiac infarction compared unfavourably with one of 16% when anticoagulant therapy was practised.

Rytand states that the mortality rate for the combined group was 28% while in patients at the same hospital treated on orthodox lines in previous years the mortality rate was 26%, and he adds that it would seem that the prognosis in a patient with cardiac infarction is worse when anticoagulants are given to someone else. Again, the mortality rate found by the ten observers whose individual results are shown in Table II among the 1,499 patients treated with anticoagulants is far less satisfactory than a mortality rate of 19% in my own series of 1,000 consecutive patients with cardiac infarction who received orthodox treatment, in that this last figure takes into account not only the immediate mortality rate following the initial attack, but also the deaths taking place during a period of upwards of ten years. Thus 590 of them had survived two years, 324 had survived four years, 151 six years, 65 eight years and 32 for over ten years (Evans, 1952). Furthermore, insufficient care has been taken in the selection of comparable cases in reported control groups, and especially in the assessment of circumstances which materially affect prognosis. Foremost among these is the association of heart failure told clinically by the presence of triple heart rhythm and radiologically by the finding of pulmonary congestion. Thus, in 118 patients with cardiac infarction showing triple heart rhythm the mortality rate was 38%, and in 88 with pulmonary congestion it was 40%, compared with the mortality rate of 19% for the whole series. The presence of heart failure, therefore, more than doubles the mortality rate in cardiac infarction; a preponderance of such patients in the control group would naturally allot a definite advantage to the test group.

TABLE II.—A COMPARISON OF THE MORTALITY RATE IN CARDIAC INFARCTION TREATED BY ANTICOAGULANTS AND BY ORTHODOX MEANS.

Authority	Anticoagulant therapy No. of cases	Anticoagulant therapy Mortality rate%	Orthodox therapy Mortality rate%	Orthodox therapy No. of cases
Peters *et al.* (1946)	50	4	21	60
Griesman and Marcus (1948) ..	75	9	35	100
Gluek *et al.* (1948)	44	20	45	44
Wright *et al.* (1948)	432	15	24	368
Wright (1953)	408	7	13	326
Tulloch and Gilchrist (1951) ..	70	23	40	84
Holton (1950)	174	22	36	256
Loudon *et al.* (1953)	75	25	41	125
Furman *et al.* (1953)	100	18	32	211
Beaumont *et al.* (1953)	71	10	37	96
Evans (1952)	—	—	19*	1,000

*This figure records deaths during a period of observation of 2 to 10 years.

THROMBO-EMBOLIC EPISODES IN CARDIAC INFARCTION

Intracardiac thrombosis cannot be told in the absence of embolism while leg vein thrombosis does not always produce noticeable signs in the affected limb. Pulmonary embolism is the best clinical yardstick to measure the frequency of thrombosis in cardiac infarction because it takes note of systemic vein clotting in addition to thrombosis within the right heart. Although some authors have reported a high incidence of embolism in cardiac infarction, 34% by Bean (1938) and 31% by Eppinger and Kennedy (1938), other writers have reported an incidence around 15% for pulmonary embolism; thus, we have 19% (Parkinson and Bedford, 1928), 15% (Conner and Holt, 1930), 14% (Nay and Barnes, 1945), 12% (Hellerstein and Martin, 1947) and 15% (Short, 1952). Ochsner and his colleagues (1950) found that an incidence of thrombo-embolism among patients in the Charity Hospital, New Orleans, had increased from less than 100 among 100,000 in the period of 1938–9 to 250 among 100,000 in 1948–9 when both ligature of veins and anticoagulants had been introduced as routine procedures to prevent this complication. Among 4,451 control cases of cardiac infarction that I have collected from the literature where the incidence of thrombo-embolic episodes has been given this event occurred in 580 or 13%, while among 1,115 patients with cardiac infarction treated with anticoagulants 105 or 9% showed the complication (Table III). The claim that deaths from thrombo-embolism can be reduced to negligible proportions (Gilchrist, 1952) by anticoagulants has not, therefore, been substantiated, and, so far, no detailed observations in patients examined at necropsy have been published in support of the statement that the difference in the mortality rate between the treated and untreated groups has been due to an increased incidence of thrombo-embolism in the untreated group (Schnur, 1953). Indeed, recently Kerwin (1953) claimed a decrease in the death-rate in patients with heart failure following cardiac infarction from 60% in the control group to 30% in the one treated with anticoagulants. The incidence of thrombo-embolic episodes in the same series was 12% and 5% for the respective groups. Seeing that the reduction in the death-rate was clearly not on account of a diminution in the incidence of thrombo-embolism, is this to be acclaimed as indicating the superiority of anticoagulants over digitalis in the treatment of heart failure?

As the clinical diagnosis of thrombosis is notably difficult, embolism may also go unnoticed. The mistake of nominating the presence of thrombo-embolism when it is not there is matched by the error of missing it when it is there, so that the incidence of this complication in any clinical series of patients depends mostly on the depth of the physician's interest in this subject and on his awareness of, or

indifference to, its occurrence, and not on the efficacy of any remedy given to prevent it. This explains why a statistical analysis of the incidence of this complication from special therapeutic measures has remained, and is destined to remain, confused.

TABLE III.—INCIDENCE OF THROMBO-EMBOLIC EPISODES IN PATIENTS WITH CARDIAC INFARCTION VARIOUSLY TREATED

Author	Control series			Anticoagulant series		
	No. of cases	Thrombo-embolic episodes No.	%	No. of cases	Thrombo-embolic episodes No.	%
Gordinier (1924)	13	3	23			
Anderson (1928)	9	1	11			
Parkinson and Bedford (1928)	100	8	8			
Levine and Brown (1929)	145	17	12			
Conner and Holt (1930)	287	42	15			
Hyman and Parsonnet (1933)	51	17	33			
Howard (1934)	165	17	10			
Blumer (1937)	175	27	15			
Master (1947)	500	29	6			
Nay and Barnes (1945)	100	33	33			
Peters *et al.* (1946)	60	10	16	50	1	2
Gluek *et al.* (1948)	44	12	27	44	3	7
Griesman and Marcus (1948)	100	21	21	75	3	4
Wright *et al.* (1948)	368	92	25	432	48	11
Tulloch and Gilchrist (1951)	84	24	29	70	9	13
Gilchrist (1952)	161	45	28	157	16	10
Russek *et al.* (1952)	623	44	7			
Russek *et al.* (1952)	1,047	63	6			
Hilton *et al.* (1949)	38	12	32	38	7	18
Holton (1950)	256	36	14	174	7	4
Loudon *et al.* (1953)	125	27	21	75	11	15
	4,451	580	13	1,115	105	9

LABORATORY CONTROL OF ANTICOAGULANT THERAPY

It is next necessary to consider the difficulty of controlling the dosage of this drug in individual patients based on estimates made in the laboratory. The coagulant property of the blood is determined in different ways; the simplest of them is not an easy procedure. Little wonder, therefore, that the results vary from laboratory to laboratory. Again, although the estimation of the prothrombin time is now the customary test the heparin tolerance test may have to be added. When these two tests were carried out by Beaumont *et al.* (1953) they found three separate phases during the course of cardiac infarction. The first phase, limited to the first two days of the illness, showed the blood to be in a state of extreme hypercoagulability. The second phase, lasting a week or so, showed hypocoagulability. This was followed by a phase of hypercoagulability variable in its degree and duration, but often lasting for a long time. Three practical lessons are drawn from these observations. First, those pledged to this form of treatment have neglected their patient if therapy is not commenced during the first few hours of the illness, seeing that the state of hypercoagulability is most obvious on the first day. This involves starting the treatment in the patient's home and demanding hospital accommodation within forty-eight hours. Such an arrangement is impracticable in the large majority of cases. Secondly, the observations point not only to the needlessness of anticoagulant therapy in the subsequent week, but also to the danger of prescribing it at such a time lest it incurs bleeding into the necrotic tissue of the infarcted area or elsewhere. Thirdly, the observations emphasize the return of a state of hypercoagulability after the tenth day of the illness, and this may last for days or even months. If it is the design of anticoagulants to prevent cardiac thrombosis it should be given in perpetuity because the threat of a recurrence or extension of the trouble remains. How inconsistent, therefore, is the doctor who prescribes anticoagulants to his patient for a time only, how unscientific are his tactics, and how certain it is that the future will condemn them. Furthermore, coagulability of the blood determined in the laboratory is not an infallible index of blood clotting in the patient. Thus, a number of examples may be met where the prothrombin time is not unduly low and yet the patient bleeds and again where the test told of hypocoagulability while thrombo-embolic incidents were recurring. Such facts supply proof once more that reactions in a test tube in the laboratory differ materially from those shown by the patient in his bed. To the difficulty of assessing the efficiency of anticoagulants because of the impossibility of assembling a strictly comparable series of patients to control the clinical results, is added, therefore, the difficulty of controlling the dosage of anticoagulants in the laboratory.

HÆMORRHAGE DURING ANTICOAGULANT THERAPY

Bleeding is the only unfavourable symptom arising directly from anticoagulant drugs and it has been seen that laboratory tests cannot obviate the risk. It has been said that deaths from thrombo-embolism can be abolished by Tromexan, but is death from hæmorrhage, which is then to become the greater risk, to be favoured on account of a more tranquil end? The place of the bleeding matters

as much as its extent; it may be of no consequence if it happens in the nose or the skin, but it is of great moment if it originates in an ulcerated stomach or intestine, in the internal capsule of the brain, in the pericardium, or in the necrotic infarcted area of the heart thereby exaggerating the injury it is meant to heal. Looking over other doctors' shoulders I have witnessed all these fatal complications taking place. Many advocates of anticoagulant therapy fail to mention the risks attendant on it; others allude casually to the occurrence of hæmorrhage in some of their patients, while others conveniently attribute the fatal mishap to a hæmorrhagic diathesis (Duff and Shull, 1949). One investigation (Editorial, *J. Amer. med. Ass.*, 1950) concerned with 15,500 patients treated with anticoagulants found that severe hæmorrhage happened in 2% of the cases. Wright and his associates (1948) reported hæmorrhage in 9% of their patients and in an additional 6% where the bleeding was not considered to have been caused by the anticoagulant; remarkable also was the finding of bleeding in 6% in the control group. Russek and Zohman (1953) reported on the questionnaire sent to leading cardiologists in the United States; serious hæmorrhagic complications were encountered by 104 or 45% of the 228 physicians in this survey, and a total of 122 deaths caused by bleeding, mostly into the brain, gastro-intestinal tract or pericardium, was met with.

Vitamin K can do little to counteract these serious episodes for irretrievable damage has been the signal for the need to use it. In this context it is rather ironical that proprietary establishments which supply a particular anticoagulant also provide their own brand of vitamin K so that Tromexan begets Synkayvite and Cumopyran its Hykinone. It causes us to think when the sale of a particular poison might be urged to boost the good offices of its corresponding antidote.

Conclusions

It is wisdom never to accept hastily the claims of newer remedies; it is duty to reject resolutely their use if they have failed after trial to reach an agreed standard of efficiency. Anticoagulant therapy has failed to satisfy any of the three demands made by the code set to test its efficiency in coronary occlusion.

It is purposeless to apply such treatment in more than one-half the patients with cardiac infarction with a view to preventing the extension of coronary thrombosis in that thrombosis is not taking place in them.

A comparison of the mortality rate in patients receiving anticoagulants with that in cases receiving orthodox treatment provides no justification for the continued use of this therapy in any kind of coronary arterial disease.

Again, a comparison of the incidence of thrombo-embolism in the test and control groups gives no support to the recommendation that anticoagulants should be dispensed to patients with coronary occlusion with the object of avoiding this complication.

Furthermore, severe hæmorrhage even under close laboratory supervision, and ungovernable by vitamin K if it is taking place in vital tissues, is frequent enough to condemn the use of anticoagulants in coronary occlusion.

Lastly, it is a sound precept in medicine never to dispense a remedy to a patient when there is doubt that it can do good and when it is known that it can do harm. That anticoagulant treatment in coronary occlusion will go the way of other discarded remedies is certain. Let it go soon. Let it go now, before remorse weighs too heavily on those who may continue for a little time longer to advocate its use.

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Indications for ACTH and Cortisone in Rheumatoid Arthritis

By J. J. R. DUTHIE, F.R.C.P.Ed.

IN the treatment of rheumatoid arthritis much has been learnt during the last four years of the contra-indications to the use of cortisone or ACTH, but indications for their administration remain very much a matter of personal opinion. However, certain aspects of the problem can now be discussed with greater confidence as a result of experience gained during this period:

(1) It has become apparent that improvement in function in rheumatoid arthritis is due to a suppression of the inflammatory reaction in connective tissues. This effect is in no way specific. The inflammatory reaction to tissue injury can be profoundly modified by the adrenal steroids irrespective of the nature of the damaging agent. This has been demonstrated in a large variety of circumstances, both in experimental animals and in human disease.

(2) There is no satisfactory evidence, as yet, that rheumatoid arthritis is due, directly or indirectly, to any abnormality in function of the pituitary-adrenal axis or to the production of abnormal steroid hormones by the adrenal gland itself.

(3) The natural course of the disease does not appear to be significantly altered in the majority of cases even by prolonged administration of either hormone.

(4) It has become abundantly clear that the continuous administration of either ACTH or cortisone, in doses sufficient to achieve complete suppression of symptoms, is impractical because of the high incidence of serious side-effects.

(5) Dose requirements may vary in the individual patient, presumably as a result of fluctuations in the activity of the underlying disease process. There is no guarantee that in a particular patient symptoms will continue to be controlled satisfactorily by a dose which proved adequate and safe in the initial stages of treatment.

(6) If treatment has to be withdrawn for any reason, not only may the symptoms of the disease recur in a severe form, but the "cortisone withdrawal syndrome" may develop—a condition characterized by exhaustion, profound weakness, anorexia, weight loss, mental depression and generalized muscular and joint pain.

(7) Experience has shown that in certain circumstances, prolonged administration of either cortisone or ACTH may be specifically contra-indicated. For example, in tuberculosis, spread of the disease is facilitated presumably by inhibition of the inflammatory reaction in tissues invaded by the organism. Quiescent lesions may become active. In infections other than tuberculosis a similar effect has been observed. The signs of intercurrent infections may be masked. In patients with a history of dyspepsia, massive hæmorrhage from peptic ulcers has occurred. Previously unsuspected ulcers have perforated. In the presence of heart disease, renal disease or hypertension, the blood pressure may rise to dangerous levels, signs of cardiac failure may appear or, if already present, become more severe. Acute psychosis may occur, especially in patients with a previous history of emotional instability. In diabetic patients, insulin requirements are markedly increased by cortisone or ACTH, and in a few instances diabetes has developed during treatment and has persisted after the hormone has been withdrawn. When the disease process has given rise to osteoporosis, hormone therapy may accentuate this condition and fractures of the long bones or collapse of a vertebral body may result. This complication occurs most commonly in post-menopausal women.

From what has been said it becomes apparent that a significant number of patients suffering from rheumatoid arthritis should not be given cortisone or ACTH because of the co-existence of conditions which increase the risk of dangerous complications. This will apply particularly to elderly patients and more particularly to women. As the average age of onset of rheumatoid arthritis is around 40, and women are affected by the disease at least twice as often as men, these limiting factors are important.

These are the main lessons learnt from experience during the last four years. It must be accepted that these hormones have no curative value and must be given continuously if their effect on symptoms is to be maintained. Rheumatoid arthritis is an incurable disease and its ultimate course is not materially altered by hormone treatment. The risk of serious side-effects increases the longer treatment is continued, although our experience to date is relatively limited. Complications become more common with increasing age. In the majority of series reported up to the present time, the duration of observation has been limited to two to three years, and a significant number of cases have terminated treatment for one reason or another. Is it likely that a worth-while number of patients will be able to continue

on these hormones throughout life on a dose which is safe and at the same time effective? The results of a trial reported recently by West and Newns (1953) do not support this view. Even if good control of symptoms can be maintained indefinitely by a safe dose, what is the ultimate effect likely to be? If the assumption is correct that the underlying disease process is unaltered and only the symptoms of tissue damage are suppressed, the wisdom of such continuous suppression is doubtful, even in patients who remain free from all complications and side-effects. Cortisone and ACTH are relatively ineffective in controlling the pain and disability which arise from irreversible damage to joints. Suppression of reactionary inflammation may, by allowing greater functional use, lead to an increase in damage of this nature. This is speculative, but the possibility requires serious consideration in reaching a decision on the ethics of continuous maintenance treatment even in those patients where this is practical.

If the dose of cortisone is kept below 100 mg. daily side-effects and complications are less common, although at this level only partial control of symptoms can be attained in the majority of cases. However, it may be argued that partial suppression of symptoms at a safe dose level is the proper compromise, giving worth-while improvement in function without entirely suppressing the symptoms which will warn the patient against over-use of damaged joints. Such a use of cortisone would be justified if it could be shown that no cheaper and safer method of treatment produced equally good results.

A clinical trial being conducted at the present time under the auspices of the Medical Research Council and the Nuffield Foundation has been designed to compare the effects of the long-term administration of aspirin and cortisone in comparable groups of patients suffering from rheumatoid arthritis. From a preliminary report it may be stated that the results in the two groups at the end of the first three months differed statistically only in respect of two features of the disease. In the cortisone-treated group the E.S.R. was significantly lower and the hæmoglobin significantly higher, but on the basis of the other objective measurements—strength of grip, joint tenderness and range of movement, the time taken to walk a fixed distance or climb a number of stairs, and a general overall assessment of functional status—no significant difference was found.

West and Newns (1953) have recently reported the results of a trial designed to provide an answer to the question whether oral administration of cortisone acetate in doses between 50 and 75 mg. daily and continued over a long period favourably affects the course of rheumatoid disease or not. The average duration of treatment at the time of publication was nineteen months. Only one patient on cortisone was able to dispense with aspirin entirely. The average requirements of the treated patients was 8 aspirin tablets daily. The results in the group receiving cortisone were compared with a group treated by other methods. No significant difference between the two groups was found. The conclusion was reached that long-continued administration of cortisone to patients suffering from rheumatoid arthritis was not to be recommended until complications which cannot be foreseen or prevented at present can be avoided with certainty.

From these studies and others in progress it would appear that even if all patients with definite contra-indications to the use of cortisone and ACTH are excluded and the dose of cortisone is kept below 100 mg. daily, complications of a serious nature may still occur. More striking, however, is the observation that the results obtained by the continuous administration of cortisone are apparently no better in the long run that those which follow the combination of full doses of aspirin with a sound basic regime of treatment.

If this review of the lessons learnt during the last four years has been fair and impartial, it would appear that the use of continuous maintenance treatment with ACTH or cortisone in cases of rheumatoid arthritis is not justified in the light of our present knowledge.

Can these hormones be applied to any aspect of the treatment of rheumatoid arthritis, even if their continuous administration is best avoided? In cases running a severe downhill course, where all other forms of treatment have failed to control the disease and where crippling deformities cannot be prevented by conservative methods, the short-term use of cortisone, or preferably ACTH, in the powerful long-acting form now available, may be justified. In such instances high doses should be used initially to control the inflammatory component of the disease and allow deformities to be corrected. These may be largely due to muscle spasm in the earlier stages of the disease and correction may be achieved relatively rapidly by the use of serial plasters when pain and spasm have been abolished. Such a course of treatment must be supplemented by appropriate physiotherapy and exercises to consolidate the gain. When these specific objectives have been attained, the dose of hormone should be reduced gradually and maximum tolerable doses of aspirin prescribed. The purpose of treatment by this method must be made clear to the patient at the outset and due warning given of the likely recurrence of symptoms during the withdrawal period. The application of this method must obviously be limited to severe cases in the early stages of the disease, before irreversible damage has become extensive, and in the absence of specific contra-indications to the use of ACTH or cortisone. The use of ACTH or cortisone to provide cover for orthopædic procedures in rheumatoid patients has been advocated. Experience in this country has been less favourable than that reported from America, and judgment on the value of hormone cover for operations and manipulations must be reserved in the meantime.

During the last year experience has been gained in this country which confirms the favourable reports from the States on the use of hydrocortisone for intra-articular injection. The action is purely local and apparently free from undesirable complications. Relief from pain and improvement in function

lasting from a few days to several weeks or even months may follow a single injection of 50 mg. Injections can be repeated without loss of effect. This method is likely to find a useful place in the treatment of rheumatoid arthritis when supplies of hydrocortisone become more plentiful. It is particularly applicable in patients incapacitated by pain and stiffness in a single weight-bearing joint. The best results have been obtained in the treatment of the knee.

Conclusions

It is my personal opinion that, in the light of our present knowledge and experience, there is no indication for the treatment of rheumatoid arthritis by the continuous administration of ACTH or cortisone. The use of short courses of either hormone, but preferably ACTH, may be justified in severe and progressive cases where conservative measures have failed to control the disease process and where severe crippledom is likely.

The local use of hydrocortisone in the treatment of single joints is likely to be accepted as a useful method of treatment, free from complications and giving worth-while relief of symptoms in a significant number.

The opinions expressed in this review of the situation are purely personal and have been reached only after considerable experience in the use of ACTH and cortisone.

REFERENCE: West, H. F., and Newns, G. R. (1953) *Lancet*, ii, 1123.

The Indications for Cortisone and ACTH in Rheumatoid Arthritis

By W. S. C. Copeman, O.B.E., M.D., F.R.C.P.

If I may summarize the experience of long-term therapy gained by my group over the last three years, I would say that cortisone and ACTH, if used properly and intelligently, can be extremely helpful, and with care need not be dangerous. Long-term maintenance presents difficulties (as do many other forms of medical therapy), but these can, in most cases, be overcome if time and trouble are taken.

We agree that under cover of long-term suppression of the symptoms of the disease structural joint changes may slowly increase, but surely this is a normal clinical risk and worth facing, if thereby the patient can be given a significant extension of pain-free and useful working life. This we have been able to achieve in 17 out of the 20 cases constituting our present trial series.

To achieve such a result, however, suitable cases must be carefully selected (some cases in recently reported trials were both unselected and had irreversible crippling present before treatment was started); and to avoid "rebound" and "withdrawal" phenomena dosage must be very gradually "tailed off" if treatment is to be stopped for any reason.

The indications for the use of cortisone and ACTH as long-term treatment we would consider to be cases of rheumatoid arthritis in which structural damage is such that function is capable of being restored to a useful degree, and which have failed to react to classical methods of treatment. There must be none of the well-recognized contra-indications present, and the patient should, if possible, be intelligent and co-operative. The dose found to be needed for adequate maintenance must be reasonably low, so that the occurrence of serious side-effects is not likely.

Indications for short-term therapy in rheumatoid arthritis will generally be to "cover" some special procedure in rehabilitation, such as manipulation. In such cases dosage must be carefully regulated, and reduced slowly and progressively. [The intra-articular use of hydrocortisone lies outside this discussion but its use in this way can be of great additional help in many cases of rheumatoid arthritis where the rate of joint improvement under oral therapy is uneven.]

We feel that following the original somewhat uncritical acceptance of steroid therapy, the recent fashionable trend is to decry the use of these hormones unduly for long-term therapy. Such criticism tends to be based on only one or two reports which happen to have achieved considerable publicity. These have over-emphasized the possible dangers and complications of cortisone therapy.

One's opinion of a remedy must depend upon what one expects of it, and Dr. Duthie and I approach the matter from different angles. He as a clinical scientist, with a somewhat "perfectionist" outlook; myself from the more old-fashioned outlook of the clinician who sees what looks like a useful therapeutic tool and tries to find out how best it can be used to benefit his patients, despite its acknowledged imperfections.

Under cortisone therapy patients still retain their imperfect joints, still suffer periodical exacerbations, and in the long run the structural damage to their locomotor system may even slowly increase under cover of these hormones. Nevertheless they can with its help be shielded from the most unpleasant effects of the disease, and so made more active, useful and happy members of society long after this would have ceased to be possible without its help.

No one, I think, has ever claimed cortisone to be a cure for rheumatoid arthritis. Unfortunately there is no real cure as yet. But many groups who have worked in this field, including my own, consider that if it is intelligently used it can be of great help in the management of this difficult disease. If we cannot find a real cure, any agent which is none the less capable of producing a major suppression of symptoms in suitable cases by virtue of an anti-inflammatory action, however non-specific, is worth looking into carefully, and learning how best it can be used.

In rheumatoid arthritis cortisone will initially reverse most of those pathological changes which still remain reversible, and suppress the activity of the disease. There can, therefore, only be two valid

grounds for serious criticism of its long-term use: (*a*) If it can be shown to be dangerous to the life of the patient; or (*b*) If it can be shown to make the patient's disease worse at any stage. (It would not even be sufficient to show that the beneficial effects were apt to wear off in time, as in that case the patient would ultimately be no worse off than prior to undertaking treatment.)

(*a*) *Danger to life.*—This suggestion is chiefly based on two patients reported by West and Newns (1952) who died whilst on cortisone treatment. There seems to me to be no valid reason, however, for attributing their deaths actually to the treatment, as one died from amyloid disease, whilst the other died of gastro-intestinal hæmorrhage after having developed a duodenal ulcer. Another possible complication is that suggested recently—but as yet quite unproven—that an atypical polyarteritis may develop in rheumatoid arthritis under treatment with cortisone.

That the symptoms of intercurrent medical or surgical emergencies may be dangerously masked has not been borne out in our experience as we have been able to diagnose cases of pneumonia, peptic ulcers, local inflammations, and one case of strangulated hernia, in cases under treatment, without particular difficulty. The only real danger in our opinion occurs if the hormone is stopped suddenly in an emergency, as then suprarenal failure may be added to the effects of the emergency.

If unsuitable cases suffering with some well-known contra-indication such as incipient cardiac failure, diabetes, hypertension, tuberculosis or psychosis are subjected to hormone treatment, disaster may follow. This circumstance, however, should never occur in the light of modern knowledge.

(*b*) *Exacerbation of patient's disease.*—The patient's disease can certainly be badly exacerbated if cortisone is used and withdrawn improperly. Everyone working in this field, however, should be sufficiently aware of the dangers of these "rebound" and "withdrawal" phenomena to be able to avoid them. There are also certain well-accepted contra-indications to its use which have been mentioned already; and we have also found that women in the menopausal zone tolerate these hormones less well than other subjects.

Side-effects.—Our experience is that if treatment is properly supervised serious side-effects do not often occur; or if they do they can be dealt with, generally without having to discontinue treatment. Some of them, such as spontaneous fracture, are of such rarity that no specific case has been reported as yet in this country.

Duthie (1952) says that unspecified side-effects occur at some stage in 50% of all cases treated. Kendall (1951) states that 50% of patients receiving a dosage above 75 mg. daily will show slight side-effects, but hardly any of these severe enough to influence treatment. Lowman (1953) is in agreement, but states that if the dosage is kept below 75 mg. daily only 21% show these unimportant side-effects. Ward *et al.* (1953) report on 46 cases treated up to two years, and of these only 9 showed side-effects (some of more than one type), but none had to have his treatment stopped.

Boland and Holten (1953) reporting on 40 patients, stated that treatment had in no case to be discontinued on account of side-effects.

In our own series of 20 cases treated for a period of up to three years (14 for more than two years), although all were unable to follow their occupations before treatment started, 17 were enabled to return to work, and in only 2 cases did we have to suspend treatment on account of late-occurring side-effects (hypertension and depression).

Finally, Dr. Duthie has drawn conclusions unfavourable to the use of cortisone from the interim report of the recent aspirin/cortisone trial conducted under the auspices of the Medical Research Council. My group took part in that, but we do not feel able to agree with Dr. Duthie's conclusions for the following reasons:

The cases selected for this series—which was not intended as a clinical trial—were early ones with few objective joint signs on which assessment could be based. These cases were, moreover, not specially selected for the purpose, which is essential if one is to obtain satisfactory results in clinical practice, but had to be selected at random in order to satisfy the requirements of subsequent statistical analysis. The dosage in the first few weeks was arbitrary, and the initial dosage unduly high in the light of modern experience. Perhaps the most important feature of all, however, had this been meant as an ordinary clinical assessment of the value of cortisone, was the statutory obligation to withdraw this substance suddenly every thirteen weeks for control purposes. This occasioned a severe relapse in nearly every case, which would have been avoided in patients who were being treated in the ordinary way.

We believe, therefore, that the clinician who has charge of patients with rheumatoid arthritis can find cortisone and ACTH of very great help in the long-term management of certain carefully selected cases. A good deal of time and trouble will have to be expended, however, if favourable results are to be maintained.

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Section of General Practice

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Cardiac Emergencies

By DAVID WHEATLEY, M.A., M.D.

CARDIAC emergencies may be classified into seven groups of causal conditions, which, in order of importance as emergencies, are as follows:

(1) Ischæmic heart disease. (2) Cardiac failure. (3) Disturbances of rhythm. (4) Pulmonary heart disease. (5) Vaso-vagal conditions. (6) Psychogenic conditions. (7) Rare conditions.

I shall deal with only two of the more important groups of cardiac emergencies.

(1) *Ischæmic heart disease.*—This may give rise to two emergencies: myocardial infarction and attacks of angina pectoris, of which the former is by far the more important. The severe attack of myocardial infarction or coronary thrombosis, immediately threatens the life of the patient—and urgent measures in the home are necessary to prevent a fatal outcome. The first of these is to combat the severe degree of shock. There is no need to dwell upon the use of intravenous or intracardiac nikethamide to revive the moribund patient; but more recently attention has been focused on measures aimed at elevating the blood pressure, when it has fallen below the critical level of 100 mm.Hg systolic. Pressor amines have been used for this purpose; and in the U.S.A., Hellerstein *et al.* (1952) showed a decreased mortality in severely shocked cases, following the use of Mephentermine, coincident with maintenance of a normal blood pressure. Similarly, Miller and Baker (1952) used noradrenaline to achieve the same result. Mephentermine is not available in this country, and noradrenaline requires an intravenous infusion, which would be difficult to administer, as an emergency measure in the patient's home. However, methyl-amphetamine (Methedrine) has been shown to be a powerful pressor agent by Bromage (1952); and I have used this on one or two occasions, with satisfactory results. My procedure is to administer half an ampoule (15 mg.) intravenously and the other half intramuscularly, repeating 30 mg. intramuscularly at six-hourly intervals for as long as may be necessary. Only one other measure needs mention and that is intra-arterial blood transfusion. This is outside the scope of the general practitioner, and in any case is of doubtful value in this condition.

Anticoagulant Therapy

The use of this treatment has reduced the mortality of severe myocardial infarction, by at least 50%. The objects are to prevent both the extension of the original thrombus, and possible subsequent embolic episodes. I wonder, also, if the exhibition of anticoagulants may not have some action in hastening the actual resolution of the thrombus itself? In support of this contention, I would quote the work of Payling Wright and her colleagues (1953), showing rapid re-canalization of experimentally thrombosed femoral arteries in rabbits, under the influence of anticoagulant therapy. Untreated controls showed no such re-canalization after several months; although Payling Wright stresses that these results in normal animal arteries may not apply to the arteriosclerotic human vessel. Be this as it may, I believe that anticoagulant therapy should be instituted at the earliest possible moment, in the patient's home. For this purpose intravenous heparin (15,000 units) must be used, for its rapidity of action; and at the same time it is my custom to administer 1,200 mg. of ethyl biscoumacetate (Tromexan) by mouth. As the action of the heparin wears off after some eight hours the anticoagulant effect is maintained by the Tromexan, which takes about the same time to exert its maximum effect. As Tromexan is completely excreted after twenty-four hours, phenylindanedione (Dindevan) with a forty-eight hour action, is more satisfactory for subsequent maintenance therapy (Toohey, 1953). The latter drug has the advantages of a smoother and more even prothrombin depression, and of only requiring prothrombin-time estimations on alternate days. If facilities are available for the latter, there would seem to be no reason for admitting such cases to hospital. It is even possible to estimate the prothrombin time oneself; and recently I have been using a small bedside apparatus which gives an accurate reading in a matter of a few minutes.

The third important emergency measure is the relief of cardio-respiratory embarrassment, in cases where there is considerable dyspnœa and cyanosis. The difficulties of obtaining oxygen promptly

in the home, may necessitate the patient's removal to hospital, but against this must be weighed the patient's fitness to survive the journey to hospital. When oxygen is available it should always be administered via a B.L.B. mask, at a high pressure of 6–7 litres/minute.

There are three other measures of less urgency. Firstly, the relief of pain; and here I consider it is better to avoid morphia, with the risk of respiratory depression, particularly in patients who are already suffering from respiratory distress. Fortunately, there are several synthetic alternatives, none as certain in its action as morphia, but usually one or other of them will achieve relief. Pethidine is probably the best known and most useful. Failing that, amidone (Physeptone) or methorphinan (Dromoran), may both be given subcutaneously; although there is evidence that the latter may have some depressant action on the respiratory centre (Glazebrook, 1952).

Pulmonary infection is a common complication in these cases, and prophylactic antibacterial treatment is an important measure. The sooner it is instituted, the better; and a wide-range antibiotic is required. I have a personal preference for combined penicillin (0·5 gramme, 800,000 units) and sulphadimidine (1 gramme); both being given by mouth in eight-hourly dosage. More expensive alternatives are Chloromycetin or Aureomycin.

Finally, associated cardiac failure will require appropriate treatment, as outlined later.

Fig. 1 illustrates some of these points. It is a chart of anticoagulant therapy, in a man of 70, who

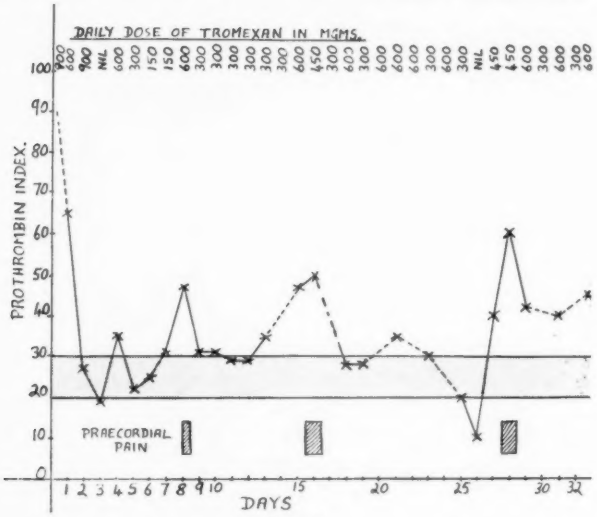

FIG. 1.

suffered a severe myocardial infarction, followed by cerebral embolism. This illustrates the uneven control obtained with Tromexan, even with daily prothrombin estimations and concordant dosage adjustment. It also shows a striking return of præcordial pain, on three occasions when the prothrombin index rose above 40%. It is essential to make every effort to keep the prothrombin level within the therapeutic range.

Angina pectoris is not an emergency endangering life but it may appear so to the patient, and the general practitioner may be called upon urgently to deal with it. The immediate treatment of the attack with coronary vasodilator drugs of the nitrite group is well established. Therefore, I would like to consider some of the more important contributory causes in relation to subsequent and prophylactic treatment.

Anæmia, of whatever cause, may precipitate attacks of angina pectoris in a patient already having some degree of arteriosclerosis; and will require appropriate treatment.

When hypertension is a causal factor, the use of sedatives in the attack is of considerable importance. One might even consider the injection of a hypotensive drug, such as Veriloid or hexamethonium, although I have never had occasion to do this.

Of endocrine causes, thyrotoxicosis is one of the most important; and sedation is again extremely useful. One might even have to consider the administration of an antithyroid drug in a prolonged attack.

At the other extreme, myxœdema may present a difficult therapeutic problem. On the one hand the hypercholesterolæmia and anæmia, which contribute to the myocardial ischæmia, will only respond to thyroid medication, whereas the administration of thyroid extract may precipitate an

actual thrombosis or infarction. I was faced with such a problem recently, in a man of 60, whose gradual development of myxœdema had been overlooked. Over a period of five to six months, he suffered from attacks of angina of effort—associated with a microcytic anæmia, resistant to iron either by mouth or injection. Following twenty-four hours of continuous anginal pain, he suffered a myocardial infarction, proved electrocardiographically. Treatment on the usual lines resulted in improvement up to the third day, when he became increasingly drowsy, often falling asleep whilst in the middle of a conversation. As there appeared to be a real risk of myxœdematous coma developing, L-sodium thyroxine was administered in small dosage. Improvement was immediate and rapid, but unfortunately the patient died after three weeks, with a sudden massive bilateral pleural effusion.

Finally, oxygen lack at high altitudes is well known to precipitate anginal attacks. I wonder also whether pulmonary insufficiency, even at ground level, may contribute in some measure to angina in a predisposed patient. Recently I saw an apparently healthy barrister's clerk of 50 suffering from increasing attacks of angina of effort, until they numbered four to five per day. Physical examination revealed no abnormalities, apart from an extremely small chest expansion of only ¾ in. After one month in the hands of the physiotherapists, this had increased to 2½ in. and he was only getting one anginal attack per week. In another similar case, I was able to demonstrate almost complete reversal of electrocardiographic changes after exercise, with the same treatment.

(2) *Cardiac failure.*—Right ventricular failure is much more common than left; but it is the latter which gives rise to the more severe and dangerous emergency. Left ventricular failure may take three forms; a subacute type resembling chronic bronchitis, attacks of cardiac asthma, and the severe attack of acute pulmonary œdema. It is the latter, usually occurring at night, that we are most concerned with. I would like to digress for a moment, and list the causes of these attacks. Hypertension and myocardial infarction are probably the two commonest causes. Attacks may occur in mitral stenosis, as also in aortic valvular disease. In acute nephritis, in addition to the hypertension, a toxic myocarditis occurs, which may precipitate attacks. Finally it should not be forgotten that drugs may cause left ventricular failure, and I have recently seen a man suffering from typical attacks of cardiac asthma, due to phenylbutazone (Butazolidin) therapy.

Respiratory infections may often precipitate an attack, and require appropriate treatment.

Before considering treatment of the two emergencies, cardiac asthma and acute pulmonary œdema, I would like to discuss the theory of causation of these attacks. The immediate precipitating cause is a disunity between the actions of the right and left sides of the heart, whereby the right ventricle pumps more blood into the pulmonary circulation than can be cleared by the left ventricle into the systemic. Thereby, pulmonary venous congestion results and œdema of the lungs occurs. This failure of the right ventricle is, in turn, caused by a sharp rise in systemic blood pressure, which precedes the attack. It seems very likely that intense peripheral vasoconstriction, which is so often a feature of these attacks, initiates and maintains this hypertension. Thereby a vicious circle is set up, and I would suggest that the acute attack is perpetuated by two factors; firstly, continued peripheral vasoconstriction and secondly, accumulation of adrenaline-like substances in the tissues, possibly of the lungs themselves. For the conditions of acute left ventricular failure can be reproduced by both adrenaline (Witham and Fleming, 1951) and noradrenaline (Fowler *et al.*, 1951).

Treatment, therefore, is aimed at breaking the chain of events leading to acute pulmonary œdema, at some physiological point. Numerous methods of doing this have been advocated:

Firstly, procedures aimed at reducing the input, and thereby the output, of the right side of the heart. It is well known that the spontaneous occurrence of right ventricular failure results in termination of the attack. The venous return to the heart may be diminished in two ways; by venesection and by applying limb tourniquets. Neither of these mechanical procedures appeals to me, although I do not doubt that they are effective. They are somewhat cumbersome procedures, also, to undertake in the patient's home.

Next we come to methods aimed at augmenting the output of the failing left ventricle, thereby relieving pulmonary blood pressure from the other side. Intravenous injection of both digoxin and aminophylline have been advocated for this purpose. I have found both drugs extremely disappointing, and have yet to see any action resulting from their use in this condition.

Then measures have been employed to prevent the patient from, literally, drowning in his own secretions. Intravenously mersalyl has been used, but again I have found it without effect; and indeed it is difficult to see how the acute attack could be relieved by its direct action. Bronchoscopy is a useful measure in hospital, but beyond the scope of the general practitioner. More recently, in the U.S.A., anti-foaming agents have been used experimentally by Rosenbluth *et al.* (1952); and Goldmann and Luisada (1952) have applied this principle clinically, in the form of alcohol-oxygen vapour. Good results are claimed, but again this treatment is not, at the moment, feasible in the patient's home.

Oxygen is an important adjuvant to the relief of respiratory distress.

Passing on to more fundamental principles, we come to the use of hypotensive agents. Hayward (1949) used tetra-ethyl ammonium bromide (T.E.A.B.) in chronic cases of left ventricular failure and suggested its use in the acute phase. In the U.S.A., Hoobler *et al.* (1952) have claimed good results from the use of Proveratrine, a Veriloid derivative.

But the likely cause of the hypertension is still peripheral vasoconstriction, and so the use of procedures aimed at producing vasodilatation is strongly indicated.

I am including under this heading, the use of morphia. There is no doubt that this drug is effective in this condition, but slow in action, when given by subcutaneous injection. Intravenous injection, as advocated by some, would seem to be a potentially dangerous procedure, in a condition where there is already a considerable degree of respiratory distress. I do not think that anybody has ever satisfactorily explained the action of morphia, in acute left ventricular failure. I would suggest, therefore, that its action is, in fact, due to its known vasodilator effect. However, other means may be used to produce vasodilatation and, in Germany, Pierach and Stotz (1952) treated their cases by stellate-ganglion block, with good results. Last year I published the results of intravenous injection of tolazoline hydrochloride (Priscol), in 2 cases of acute pulmonary œdema; and of the oral use of the same drug in a number of cases of cardiac asthma (Wheatley, 1952). I am now awaiting an opportunity to try the effect of a pure vasodilator, such as nicotinic acid, or its more effective successor, β-pyridyl carbinol (Ronicol).

It must be remembered that, in addition to its direct vasodilator action, Priscol is an adrenolytic agent. However, both these actions are comparatively weak; and there is also the disadvantage that its action by intravenous injection is only transient, being over in a matter of three to five minutes. However, this may be sufficient to break the vicious circle. As I have postulated accumulation of adrenaline-like substances as a causal factor, it would seem logical to use other and more powerful adrenolytic drugs. For this purpose I have used Hydergine (hydrogenated ergot alkaloid preparation), and propose to use benzodioxane on a future occasion.

Figs. 2 and 3 show the effects of intravenous Priscol and Hydergine, in two separate attacks of acute pulmonary œdema, occurring in a man suffering from essential hypertension. As he had been observed for several years before the attacks occurred, his usual blood-pressure readings were known. On both occasions there was a sharp rise in both systolic and diastolic pressures in the

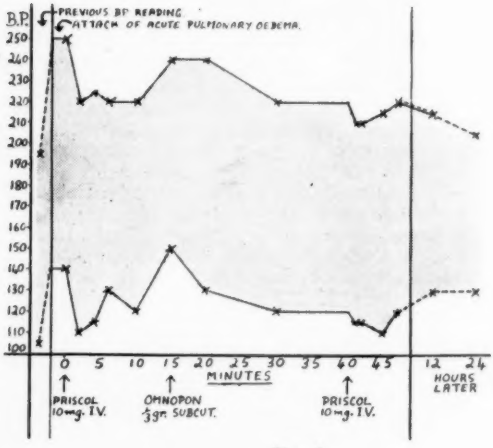

FIG. 2.

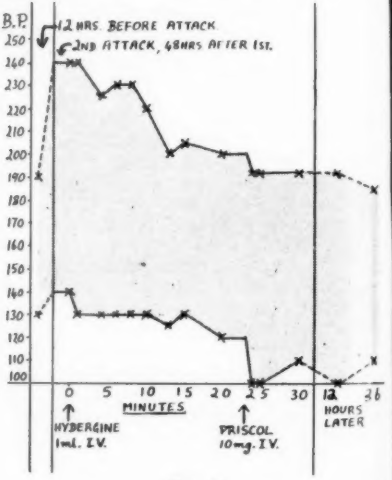

FIG. 3.

attack. Injection of Priscol 10 mg. (I now consider this to be too small a dose), produced an immediate fall in blood pressure, but this was not maintained and the attack was not relieved. Injection of Omnopon (papaveretum) produced a slow gradual fall in blood pressure, but a further injection of Priscol was required to terminate the attack. On the second occasion (Fig. 3), injection of 1 ml. of Hydergine resulted in immediate relief of symptoms and a gradual fall in blood pressure. Priscol was again required finally to terminate the attack.

Emergencies due to right ventricular failure are mainly due to secondary effects upon pulmonary function. Respiratory distress is manifested by cyanosis and dyspnœa. Pleural effusion may be sudden and massive, and may necessitate paracentesis as an emergency measure. Massive œdema and ascites may cause urgent distress to the patient, but the latter does not require immediate paracentesis although it may contribute to respiratory distress, by pressure on the diaphragm. Treatment of these conditions is well established on conventional lines; oxygen therapy, cardiac glucosides and mercurial diuretics. Sedation and analgesia are also important measures. Complicating pulmonary infections will require appropriate antibacterial treatment.

A degree of anæmia is not at all uncommon in cases of congestive failure, and it is surprising how the patient's cardiac condition improves, when it is treated. This is well illustrated by a male patient of mine, aged 80, with long-standing aortic regurgitation, who developed auricular fibrillation and congestive failure. Although this was adequately controlled, he became more and more lethargic, sleeping most of the day and only being roused with difficulty, for meals and conversation. His Hb level was found to be 50%, with an iron deficiency type of anæmia. There was no response to iron by mouth, but a rapid recovery followed intravenous injections of saccharated iron oxide, which raised the Hb level to 89% in three weeks.

Conclusion.—The essence of treatment in most cardiac emergencies is embodied in a comprehensive knowledge of the treatment of ischæmic heart disease and of cardiac failure.

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DISCUSSION ON THE MANAGEMENT OF THE ALCOHOLIC IN GENERAL PRACTICE

Dr. J. Yerbury Dent: On entering general practice, my father handed me those addicts who had been a trouble to him for many years and I had plenty of opportunity to get to know them and try various ways of giving them apomorphine. I thought I might sicken the drinker of alcohol by limiting his intake to that and nothing else and by following each potation with a vomit induced by an injection of apomorphine I would produce a conditioned aversion.

By giving apomorphine before alcohol an aversion to it can be produced in most people but it is very transient and slight and sometimes there is none at all. Some alcoholics are not sick even with big doses of apomorphine, up to half a grain intramuscularly, and I have had one who had no sense of smell and did not know whether his drink contained any spirit or not and so could not develop an aversion to it. The success of apomorphine does *not* depend on a conditioned aversion and it is the only treatment of addiction to alcohol that is successful in the treatment of addictions to morphine and other cerebral sedatives.

It is also useful in hysteria and in the possible biochemical disturbances which may accompany anxiety and misery, and in puerperal mania. It has also been given for the morning sickness of pregnancy and for seasickness. I have had many alcoholic patients with albuminuria up to 2% which has cleared up entirely during the week's treatment. I gave it to myself when I was in acute misery, with satisfactory results: I put these down to removal of undigested food and the sleep that followed. A post-partum maniacal case that had shrieked for two days and nights and refused to feed her baby and tried to destroy it because she said it was dead, was given one-tenth of a grain and she was asleep in ten minutes. I woke her an hour later after having given the baby the breast and she was perfectly sane and she had not vomited at all. She remained sane and has had two more children without trouble. A woman my father had known from birth, aged 40, had been married for eighteen years. She and her husband had longed for a child and had gone everywhere for advice. They were very much in love but unhappy because of their longing. She was waiting for him to come home to dinner when she was rung up by the police to tell her that her husband had shot himself through the head in his car. She went mad. She tried to throw herself out of the window and by the time I got to her she was fighting with her maid, the porter of the flats and her mother, her clothes were in ribbons and she was shrieking. I gave her one-tenth grain of apomorphine and she was sick and then slept. I returned two hours later and gave her a second dose. She again was sick and slept. She was perfectly sane the next day, identified the body, went through all the beastliness of the inquest and never needed any further medical or psychological help; not even after reading a letter her husband had left for her saying that he had that afternoon discovered that he could never have a child and perhaps it was not too late for her to marry again and get one. Cases like these made me think that some readjustment in blood chemistry had been produced through stimulation of the hind-brain.

Feldmann (1953) in Geneva, who has treated over a thousand addicts with apomorphine under a government scheme, has published the effects of apomorphine in normalizing the percentage of

various substances in the blood serum. The question now is—is the humoral imbalance the cause or the result of addiction. Alcohol by anæsthetizing the repressive action of the fore-brain on the diencephalon could temporally produce greater activity in the latter while the alcohol was present.

Treated alcoholic patients will relapse if they take alcohol even in small doses. I had one patient who drank heavily for years after being heartlessly jilted and, though a publican, had remained teetotal for eleven years after treatment and then, becoming again engaged to be married, was persuaded by his lady to take a glass of sherry with her to drink to their mutual happiness. He protested that he dared not take it. He had told her of his previous troubles but she said that he surely could trust himself now and she would not marry a coward and persuaded him to drink. The next day he drank a bottle of whisky and then more the next, and she threw him over as she would not marry a drunkard and he drank still more and had to be treated again. He was afterwards teetotal but remained a bachelor.

As I believe that apomorphine is much more quickly eliminated from the body than alcohol and as alcoholics so suddenly relapse even after small doses, I then continued the apomorphine injections for two days after stopping the alcohol, which I still give in the first stage of the treatment, and got better results, even if they vomited their soft drinks, and so risked developing an aversion to them.

I also found that morphine and heroin addicts could be detoxicated in a week with very slight deprivation symptoms under apomorphine and that even these slight symptoms could be prevented almost entirely if alcohol were given with the apomorphine in exactly the same way as if I were treating an alcoholic. It is five and a half years since I treated my first morphine addict in this way and he has not relapsed.

These and many other different cases destroyed the theory that the production of a conditioned aversion was the main effect of apomorphine.

Then I began giving apomorphine sublingually or in the pouch of the cheek. Now I treat quite 75% of the addicts who come to me with apomorphine by mouth.

Most general practitioners at present do very little for their alcoholic patients. This is because students are taught very little on this subject. In spite of the enormous literature on addiction, very little gets into our medical textbooks. The public, thanks partly to the exertions of Alcoholics Anonymous, is being educated and it is now realized that addiction is a disease, however much drunkenness may be a moral lapse.

The general practitioner can do a great deal for his addicted patients.

First, he has to diagnose between the self-indulgent drinker, and the alcoholic addict, the compulsive drinker. The former can be helped by aversive treatments such as the conditioned aversion following emetine plus alcohol, as favoured in the United States or the Antabuse of Scandinavia, which punishes the taker of alcohol with acute acetaldehyde poisoning.

I have found that some excessive drinkers can cut down, or even cut out, their drinking by taking *carbachol* 1, 2, or 3 tablets, taken before lunch, tea and bed-time. I should like to hear more about this most physiological of the fore-brain sedatives.

Antabuse does not remove craving, the necessity for drink. I have met two cases, both addicts, both married to women doctors, who conscientiously saw that their husbands took their Antabuse regularly. Their craving was such that this did not stop their drinking, and one developed large scotomata and auditory neuritis before giving up his Antabuse; the other died of acetaldehyde poisoning a month or so after his marriage.

If it is decided to treat a drinker with Antabuse the doctor should carefully try out the effects of alcohol after small doses and not distribute it in the carefree way so many scatter their barbiturates.

Barbiturates should not be given to alcoholics except during delirium tremens, as they may easily switch their addiction to the stronger drug. There are, I am sorry to say, proud teetotal members of A.A. who now take their daily whack of phenobarbitone.

For the compulsive drinker at present I know of nothing as effective as apomorphine in removing the compulsion, the *need* for alcohol and in the milder cases of addiction, those who still eat fairly well, who have not developed polyneuritis and those who can be without alcohol for a week or more occasionally with no marked jitteriness or fear of D.T.s. These should be given apomorphine sublingually.

One-tenth of a grain tablet by Parke, Davis or B.D.H. (other brands may not be so soluble) is placed under the tongue or in the pouch of the cheek and, though it breaks up almost at once, it and the saliva are swallowed only after ten minutes. One hour later two tablets are taken in the same way. After a further hour three tablets, and so on, increasing by one tablet every hour until dose X tablets is reached, which produces vomiting. After this ¾ of X is taken every two hours while awake until the next day when the dose is pushed up again by one tablet every hour until a second vomit is produced by dose Y. After this ¾ of Y is given every two hours while awake for three days and nights from Y. But if Y is not greater than 1½ times X then two days and nights from Y will be sufficient.

An overdose cannot be taken by mouth because it would automatically remove itself, but I have known rare patients that have not been sick with a dose of 3 grains (30 tablets) at hourly intervals: all they complained of was that they felt a little dizzy. I do not advise patients to go further than 20 tablets, i.e. 2 grains two-hourly for three days and nights.

During the treatment the patient takes ordinary food but *no* alcohol. He stays indoors while he is experimenting to find his vomiting dose but once this is found he may go to his work as usual if he can arrange to be undisturbed for ten minutes every two hours. He need not be wakened for his medicine but should have little heaps of it by his bed so that if, and as soon as, he wakes he can put the next heap into his cheek and go to sleep again.

During the first twenty-four hours he may have a craving for drink, in this case he should stay in bed and on the second day his craving will be much less or have gone entirely but he should continue for the full three or four days.

This is the treatment of choice for those who relapse after the more drastic treatment by injection. There are rare cases who develop sensitivity to apomorphine with swelling and soreness of the tongue and mouth. I have never seen this at the first treatment but I have seen it in relapsed cases and I know of no method of combating it. Antihistamines relieve it only slightly.

The mouth treatment can be given even by the most busy general practitioner and it is safe and highly effective if the patient carries it out honestly. If there is any doubt that he will do this his wife or a nurse may give him the necessary moral support.

All alcoholic cases need glucose and vitamin B_1 100 mg. daily, and possibly the whole B complex. They should be encouraged to take wholemeal bread with jam or marmalade, Bemax and Marmite. It is often advisable, if possible, to give them these for a few weeks before any apomorphine treatment. They are then less likely to develop D.T.s and their polyneuritis is combated. Some suffer from pellagra, some have Korsakoff's or Wernicke's syndrome and need nicotinamide and B_{12} as well as B_1 and the G.P. should see that they continue to get the necessary vitamins after they return to normal life.

The compulsive drinker who has polyneuritis, who cannot face life for a day without alcohol, and therefore who is certainly liable to have D.T.s, should be treated with apomorphine by injection and alcohol by mouth in a home or hospital. If the G.P. has the time, and it should not need more of his attention than an ordinary obstetric case, he should give the ordinary intramuscular apomorphine treatment in a nursing home under expert nurses. The dramatic change in his patient in under a week is very rewarding and interesting to watch.

At present there are in the United Kingdom only about half a dozen beds (in St. Luke's Hospital, Woodside Avenue) where efficient treatment is available under the National Health Scheme. Some degree of psychotherapy is certainly very helpful. I always give my patients a few minutes waking suggestion as a slight insurance against their taking alcohol by mistake. Thus I tell them that they will not miss alcohol—that they are proud of not needing it and are happy without it—that they love their families and enjoy their food. A lot of trite remarks perhaps, which their conscious critical mind distrusts but would like to accept. The best way of enabling them to do this is to repeat these suggestions while they are reading a newspaper aloud. When a man is reading he is to a certain extent in a trance—a trance that he has already learnt to achieve. Waking suggestion is the easiest and simplest form of hypnosis.

REFERENCE

FELDMANN, H. (1953) *Brit. J. Addict.*, **50**, 59.

Dr. J. A. Hobson:

I believe it is true that alcoholics are never cured by psychoanalysis alone, and that the time for analytical treatment, if it is needed at all, is only *after* the alcoholic has become teetotal. But though psychoanalytic technique is unnecessary, even unwise, psychotherapy of some form is still essential if we are to treat our alcoholics adequately. Psychological factors in the doctor-patient relationship are the most important determinants of success in the treatment of the patient. And any G.P. who is worth his salt is capable of using psychotherapy of this type—and should be capable of using it successfully with his alcoholic patients.

Many alcoholics are coerced, unwillingly, by their relatives to visit their medical practitioner, and consequently are often suspicious and guarded, sometimes openly antagonistic, but unless the G.P. can win the confidence of these patients, he fails.

If the patient is fully co-operative and really desirous of cure the way the first interview is conducted is all-important in determining the ultimate success of treatment—at least as important in deciding what drug to use in subsequent therapy.

Winning of the patient's confidence and co-operation should be the primary aim of the first interview and thoroughness of examination and accuracy of diagnosis must take a place of secondary importance. Over-questioning, and over-meticulous psychiatric history-taking in the first interview loses many possibly treatable patients.

Accuracy of diagnosis and assessment of causative factors in a case of alcoholism is certainly important and of great academic interest, but it must be postponed if there is any risk of diagnostic history-taking antagonizing the patient. It is doubtful whether it is possible to make a reliable estimate of diagnosis and ætiology whilst the patient is still drinking.

Most alcoholic patients show some evidence of psychological abnormality, but it is seldom, if

ever, possible before treatment to determine whether the alcoholism is secondary to the neurosis, or the neurosis to the alcoholism. I feel that the latter order of events is the commoner one. Psychoanalytic friends often criticize my methods of treatment by the following type of argument:

In taking alcohol away from your patients you are doing nothing to remove the unconscious mechanisms which have led to the alcoholism. The energy of these repressed complexes will find some other outlet—perhaps something worse than alcoholism—or more severe neurosis or psychosis will develop. This is a hypothesis which is not borne out by observed facts. I can say with confidence that all my successfully treated cases have become less nervous, not more, after treatment. Frequently symptoms of anxiety or tension have disappeared, and I have had one or two cases of combined alcoholism and sexual perversion in which, without any analytical procedure, the perversion ceased after the alcoholism had been treated. I have not known the reverse to happen.

Often of course—as one would expect in those cases where neurosis has been the basis of the alcoholism—the patient is left with psychological symptoms (usually improved) after he has become teetotal. In such cases appropriate psychiatric treatment is given—but not until *after* he has stopped drinking. In my opinion it is just as pointless to attempt to treat an alcoholic's neurosis whilst he is still drinking, as it would be to treat his cirrhosis or his peripheral neuritis.

When an alcoholic first presents himself for treatment he almost invariably has a strong sense of shame and failure but is on his guard against moral accusations or exhortations to use his will-power. An alcoholic doctor described the state as follows:

"The true addict has an intense dislike of himself, his habits, his behaviour, his reaction to his friends and normal individuals. He is the most supremely unhappy of mortals. He thinks life is finished, he imagines himself guilty of unspeakable infamies, he plumbs the depths of human experience; and yet the dreadful craving is always there for the drug which has been responsible for his misery."

The aim of the G.P.'s first interview should be to combat in some small way this attitude of the patient towards himself, the world in general, and his affliction. He must be surprised. He half expects a moral exhortation—there must be no hint of it. He expects to be asked to use his will-power—instead he is told that his will is quite powerless where alcohol is concerned—that he is suffering from an illness as a result of which he can no more by an effort of will stop drinking alcohol than a normal person could stop drinking water.

He must be given some ray of hope for the ultimate future that there is still a possibility that once again he will be able to live a reasonably happy and socially useful life. Above all he must be left to feel that he is an individual—an individual still of some interest and perhaps even worthy of some respect. I believe this point of "interest" is of real importance in winning the confidence and co-operation of any patient, alcoholic, neurotic, or physically ill, and one which I always stress to medical students in advising them how to develop a therapeutic relationship towards their patients.

The patient must be led to feel that he is no longer alone. The absolute aloneness which most alcoholics experience can be one of the most terrifying of their symptoms. Let him feel that at last there is someone prepared to be a friend to him—that he is no longer alone. To the same end it is helpful, preferably at the first interview, to introduce him to other alcoholics under treatment or who have been treated, preferably someone of similar intelligence and background—partly to inculcate a group feeling, partly as an object lesson that alcoholics are treatable, and partly to foster a sense of responsibility and usefulness in the treated alcoholic. For similar reasons I prefer to treat alcoholics in hospital in groups of two or three at a time rather than individually—moreover usually the treatment I give in hospital is rather unpleasant and a patient does not feel quite so sorry for himself if he sees in the next bed someone feeling equally miserable.

It is important to convince the patient early in one's handling of him that he is indeed an addict—that he will never be able to take an occasional glass of sherry without drinking too much. Treatment can make it fairly easy for him to become teetotal, but no treatment can enable him to become a controlled drinker. If after treatment, with apomorphine or anything else, he drinks at all he will inevitably relapse into alcoholism.

The patients who have suffered most as a result of their alcoholic excesses are those most likely to accept the belief that they are alcoholic addicts. The man of middle age who has lost his health, his earning capacity, his wife and his family, his social status and the respect of his friends, is much more likely to believe he is an addict than is the young student who has been reprimanded at college for his drunkenness. Unlike nearly every disease in the medical textbook, the likelihood of benefiting an alcoholic with treatment improves with increase in age.

Often a patient's relatives try to persuade me to ensure his admission to hospital by some trick or subterfuge. This I always refuse. If I am to be of any permanent help to the patient I must keep his confidence and trust. To be detected in untruths or tricks would ruin this confidence, consequently I always try to answer patients' questions as sincerely and accurately as possible—whether the questions are about the probable effects of continuing drinking, or about the unpleasantness of the treatment he will receive if he comes into hospital. The only hope of getting the truth from an alcoholic is to be truthful in return. Anyone who tries to influence an alcoholic by lies will certainly lose: the alcoholic is more practised in deceit and lies with greater facility.

JOINT MEETING No. 3

Section of Orthopædics with Section of General Practice

Chairman—H. L-C. WOOD, M.S., F.R.C.S.
(President of the Section of Orthopædics)

[*December* 1, 1953]

DISCUSSION ON THE PLACE OF ORTHOPÆDIC SURGERY IN THE MEDICAL CURRICULUM

Dr. D. T. Rowlands: I shall discuss the place of orthopædics in the medical curriculum from the point of view of the general practitioner with an orthopædic training.

Two years ago I was appointed to a practice in the West Wickham area of Kent, with a list just over two thousand five hundred. I had previously been Orthopædic Registrar at my old teaching hospital for three years.

As a result of my experiences in general practice over the past two years I am firmly convinced that a large number of the commoner orthopædic conditions can be efficiently and adequately treated in the patient's own home by the general practitioner, provided always that he has a basic knowledge of orthopædics comparable to his knowledge of pædiatrics, cardiology and gastro-enterology. This knowledge must be gained during his undergraduate clinical training and supplemented by post-graduate week-end revision courses.

Between 1.9.51 and 30.8.53, 1,619 new cases were examined either in the surgery or in the patient's home. Of these, 173 (10·7%) were frankly orthopædic, excluding all fractures, and all cases of rheumatoid arthritis, although I consider that a large part of the treatment of the latter condition is essentially an orthopædic problem. Of these 173 cases only 39 (22·5%) had to be referred to Consultant Outpatients, although 15 more were referred for the provision or replacement of simple surgical appliances (Table I).

TABLE I

	Total	Referred to hospital	
Ankles	10	2	
Backs	88	15	
Feet	13	2	
Hands	4	—	(excluding 2 cases of Dupuytren's contracture)
Knees	27	9	
Hips	6	5	
Osteomyelitis	3	1	
Shoulders	13	2	
Tennis elbow	5	2	
Carpal tunnel syndrome ..	4	4	

Some of these groups warrant more detailed description.

(*a*) *Backs.*—This was by far the largest group. Of the 88 cases, 77, 39 male and 38 female, showed lesions in the lumbar area, 9 in the cervical and 2 in the thoracic. In addition 4 cases had malignant metastases, the sites of the primaries being two in the breast, one in the stomach and one in the prostate.

I classified, and therefore treated all these conditions as disc lesions or ankylosing spondylitis. The diagnosis was based on the history, clinical examination and radiological appearances, the latter being especially important in differential diagnosis. I was fortunate in that my local hospitals allow direct access to their X-ray departments.

In the 39 males with lesions in the lumbar spine, treatment was essentially conservative in principle. 10 cases were severe enough to warrant complete bed rest. 29 were able to continue at work. 12 patients complained of backache only, while 27 had sciatica also. One case, the most severe, recurred twice in four months despite full precautions, and required laminectomy, while another four had mild recurrences due to inability to combine the regime advised with the activity necessary for their work. 12 patients required polo belts: these were the only cases referred to hospital, except the one who needed laminectomy.

Of the 38 female patients, 5 required a specially constructed surgical corset, while another 4 were able to have their existing corsets modified.

The regime is a simple one once the diagnosis is made. Depending on the severity of the symptoms, bed rest or rest at home or local rest (i.e. a plaster of Paris jacket in the case of the lumbar spine—I applied two—or a Thomas's woollen collar in the case of the cervical spine—three were applied) is the first stage. In addition a liberal quantity of Tab. Codein. Co. is supplied to the patient as well as a list of do's and don'ts. Once the acute stage is over a decision must be made as to the necessity of a permanent support, e.g. polo belt or plastic collar.

Cervical spine: Of the 9 cases of cervical spondylosis 4 were male and 5 female. 2 had to be admitted to hospital after failure of domiciliary treatment with a Thomas's woollen collar and analgesics such as Tab. Codein. Co. They both responded dramatically to head suspension in slight flexion, one with four, and the other with five daily treatments.

Thoracic spine: Both cases were treated effectively by complete bed rest on a firm mattress. In one case this was achieved by placing the middle leaf of the dining table under the mattress and in the other the door of the garden shed was used for the same purpose.

(*b*) *Hips.*—Of the 6 cases presenting themselves with painful hips 5 required hospital treatment. 3 needed operations to relieve the pain, and one—an old untreated septic arthritis—had to be provided with a built-up shoe. Another was referred for consultant help in the diagnosis. He subsequently improved greatly with physiotherapy. The last case—a hypertensive old man with two stiff hips—is managing well enough on analgesics only. Hip disease which can benefit from non-operative treatment should be referred to the Hospital Physiotherapy department, where patients can obtain great benefit from apparatus too bulky for home use, although some forms of treatment, such as sling-supported exercises, can also be arranged at home.

(*c*) *Patients complaining of their knees.*—27 such cases were seen, of which 9 had to be referred. 5 showed evidence of cartilage injury. All were referred to hospital. The "first offenders", of which there were 2, did not need operation but by attending hospital got themselves on the books of the Orthopædic Department, thus saving time in the event of a possible recurrence.

2 patients with loose bodies were likewise referred.

There were 12 osteoarthritics. 10 were treated at home, but 2, who were very obese, were referred for more intensive physiotherapy.

There was 1 patient with collateral ligament strain who was not referred.

7 children presented with knock-knee. 3 had to be referred for alterations to their shoes, i.e. 3/16 in. inner wedges. By the time I saw the other 4 I had trained one of the local shoemakers to adjust the heels of the shoes.

(*d*) *Shoulders.*—13 cases seen. Eight were supraspinatus syndrome. Of these 2 were referred for treatment at local hospitals after failure to respond to treatment at home. Of the remaining 6, 2 required analgesics only, whilst the remaining 4 responded dramatically to local infiltration with 1% Novocain.

There was one partial tear of the supraspinatus tendon; the result of a football injury. This was treated by active exercise and daily supervision in the surgery.

Three more of this group were acute peri-arthritis going on to frozen shoulder. The regime in this type of case was rest and analgesics in the acute stage followed by active exercises as soon as the pain had subsided. It is my impression that putting the joint at rest as soon as possible and not prescribing embrocations as so often happens, saved these patients months of incapacity and possible manipulation although I admit that the numbers are far too small to judge fairly. The results in these 3 cases of complete recovery in six to ten weeks is suggestive.

The last case in this group was a subluxation of the acromioclavicular joint. This was treated by rest in a sling for six days with the liberal use of Tab. Codein. Co. and then active exercises. This patient was playing wing half-back in six weeks.

(*e*) *Hands.*—4 cases were seen. One was a snap finger which required operative division. 3 were osteoarthritic hands secondary to mild rheumatoid. All 3 were effectively relieved with wax baths carried out at home after a demonstration in my surgery.

Conclusion.—It is the duty of the general practitioner to relieve pain and to avoid the loss of working capacity of his patients whether they be housewife, wage-earner or school child; furthermore he owes it to his consultant colleagues to relieve them of all unnecessary outpatient consultations. It is also most important to the patient to save attendance at Hospital Outpatients whenever possible.

From my experience as a clinical assistant in the Physical Medicine departments of two of the local hospitals I have gained a strong impression that most general practitioners are reluctant to treat any of the conditions I have described. I believe that the main reason is that they have never received an adequate orthopædic training.

Finally, the application of a basic orthopædic knowledge to conditions seen in general practice thereby relieving pain and saving loss of the patients' working hours is, I think, one of the most satisfying aspects of general practice in a national health service.

Mr. **Julian Taylor** [*Abridged*]: The study of orthopædics in medical education is very properly a matter of concern to the leaders of this branch of surgery, and it is not the first time that a meeting has been devoted to it. Indeed, Sir Harry Platt delivered a thoughtful Address to the British Orthopædic Association on this subject eight years ago (1945, *Lancet*, ii, 643).

I shall begin with a short statement of how I think pre-qualification medical education should be conducted.

The design of medical education.—Sir Harry Platt's Address is concerned with the place of orthopædics in medical education and in the regional hospital services. Though obviously allied the problems are distinct, for the former concerns the moulding of the doctor mind, the latter the efficient use of trained specialists in a hospital service. One can imagine for example a service in which all patients would be dealt with with the highest efficiency by staffs, each member with very restricted interests. Such an organization, if a teaching hospital, would perforce have to treat its students as if they were on a production line. Each member would add something until the student should emerge a doctor, packed with the latest information on all medical subjects and, like the finished motor car, obsolescent from his day of qualification. I have read somewhere bitter complaints of the poor training that engineer and fitter apprentices get in big workshops where machines do all the work, the essence being that there is no attempt to train the apprentice's mind. Such a conception applied to medicine would become a technical school with a cram course added.

Medical education should be of the university type. The scientific aspect of it is now on so high a plane and has resulted in the past two or three decades in a rapid progress that permeates all branches. So that the ordinary student of medicine, who perforce learns all branches, is faced with the absorption of a body of information that is advancing in something that may be compared to a geometrical progression. There are now so many established facts, so much elaborate theory, that in my opinion it is impossible for any mind, however young and active, of however high a quality, to absorb the whole vast curriculum in three clinical years. The attitude of authority seems still to be that, regretfully it is true, more and more must be added to the curriculum, reminding one of the Regency buck—was it Beau Brummell?—who just demanded more curricles.

With the enormous increase in the scope of its studies, medical education must therefore, I think, become more and more concerned with the principles, scientific and otherwise, that underlie and guide our art; less and less with the minute examination and memorizing of facts and the results of progress. A mind that has been trained to rely on primary considerations and principles is better trained for the evaluation, assimilation, development, of new facts, than is one already packed with new but inevitably obsolescent conceptions and theories. I therefore deplore any attempt at making a complete technical, factual, or theoretical, whole of any student's education. The plea is sometimes advanced that students' education must be comprehensive so as to make them safe for the public. The spoon feeding that is the consequence of such an attitude has exactly the opposite effect, for it crams into his head enormous numbers of facts including nowadays powerful and dangerous therapies, and fails to help him to the breadth of mental capacity which alone enables him to appreciate what he is studying.

Unfortunately medical education is necessarily associated with the learning of large numbers of incompletely explained facts. Nevertheless the function of the study of such facts is to exemplify principles. Once the principles are established in the student's mind the facts may safely be relegated to the haze of the half-forgotten until they are needed in the elucidation of particular clinical problems. This is important, for a corollary is that no student should have cause for complaint if a group of facts should have been omitted from his training, for another group may well have established the same principles. A medical school should be like the other faculties of the university, where the teacher's task is to place before his students in whatever detail he chooses some aspect of his work upon which he is an authority. At Cambridge there have been Rutherford, Thompson, Trevelyan, Adrian, and nearer home I remember Ramsay, Starling, Baylis, Charles Bolton, Rose Bradford, Trotter. In lesser stature our medical schools are full of such people. It is the student's task to collate what has been placed before him with his reading and with his own usually intelligent appreciation of it to integrate what has been made available for him. This is the most important, the indispensable, part of a good education for all kinds of doctors.

Medical education, however, is different from that in some other faculties in one way. As we conduct it, it has the element of apprenticeship, for students as soon as they enter a hospital begin to make contact with the patients who will be their life's work. The importance of this is many-sided but two very striking features at once emerge. The first is that he soon finds that his own special senses, which he probably thought infallible, need training. The second that the subject of his study is no longer enclosed in test tubes but in living persons and he learns about the doctor-patient relationship.

Apart from a general proposition that the whole practice of the hospital should be available for the students' study, and that the hospital staff should be there to teach them, little more is necessary.

If he is properly taught on a basis of principles and is whenever it is possible given or enabled to deduce a reason for everything, it does not matter much in which departments he gets his patient contacts. Equally obviously the simpler the problem at the start the easier it is to instil the essential

principles of our work. With such a foundation the specialisms find little difficulty in dropping into place in the growing unity of his education.

Education in orthopædics.—Orthopædics is no longer even principally concerned with the straightness of children any more than surgery is confined to the handiwork that gives it its name. Orthopædic surgeons have laid claim to the exclusive practice by them of a great deal of surgery. It suffices to say that orthopædics deals with a large proportion of the injuries and diseases of the limbs. Thus there are included the fractures, some of the diseases of joints, and the deformities of the original orthopædic specialty.

Here we find two extremes: There are the fractures and other common injuries, and with the principles of the recognition of these and with their treatment the student must be familiar. There are thus large parts of orthopædics with which he must be acquainted by practical experience, and it is obviously essential that these must be included in his training.

Then, at the other extreme, there are the deformities of which he need merely know the existence. His grounding in principles tells him that they may be of congenital origin or due to some cause like paralysis which may be more important than the deformity, and it also will provide him with the means by which the congenital may be distinguished from the acquired. It follows that there are also large parts of orthopædics that are of little importance to him. The technical methods employed in congenital dislocation of the hip or in Judet's arthroplasty are of little importance to him, of no more and no less importance than the technique of removing the stomach, the lens, or a meningioma. But if his interest is aroused in any of these exponents of the art will be at hand, and it is highly desirable that such an interest be in fact aroused during his education, though it matters little which one.

To return to fractures, that part of orthopædics which undoubtedly must be included in his training. Nearly twenty-five years ago, reflecting that the management of fractures in my hospital was then unsystematized, I brought forward a plan that each firm should have a fracture clinic meeting at a different time from its other activities. This was accepted and since then each firm has carried this on. In its original conception, the plan was that each outpatient should be entrusted to a dresser who would himself conduct such part of the rehabilitation as was suitable and in general see the patient through. Thus once a week my dressers see about 20 fractures in varying stages of healing and supervise their recoveries. We have always had a member of our staff interested in fractures to whom we could turn in difficulty and now we have officially in advisory charge our orthopædic surgeon. In the last five years 300 Colles' fractures and 126 Pott's fractures have been guided back to recovery by our students, with an average period before return to full work of nine and fourteen weeks respectively. It is Mr. Squeers' doctrine reversed—"When you goes and does it you knows it"—but it is more than that for it has the wider implication that all our students become personally familiar with the principles of the recognition and treatment of fractures and many other injuries of the limbs.

Our system is not ideal. It began at a time when under the leadership of Mr. Gwynne Williams most of our younger surgeons were interested in fractures. This is not so now. Since the end of this last war I have left my fracture clinic to my assistant surgeon who is so interested, but maybe our fracture clinics will pass more and more into the hands of our orthopædic surgeon working through our registrars, though this has not yet happened. The important thing is that all students must be personally and practically familiar with the management of fractures and other limb injuries, and if one spreads the work out through all the firms the problem is easily manageable.

So far as inpatient work is concerned I do not think it matters whether a student dresses for an orthopædic surgeon, a general surgeon, a neurosurgeon, a plastic surgeon, or any other specialist. Wherever he works he will learn the principles of pathology, examination, and treatment, and in his subsequent student years he will have the whole hospital staff to guide him while he educates himself.

In such a plan of medical education the specialties fit themselves naturally into place though it is true they are getting a little cramped for space and time.

I am now able to state my opinion that though it is necessary to organize our surgical services, our medical education suffers when we try to organize and compartment it to the same degree.

I close with a reference to the examinations that loom so large in students' minds. In my opinion it is the examiner's task to find out not so much what the candidate knows but what, after his training, he is capable of knowing. For medicine is advancing at such a gathering speed that though qualification legally means being qualified to practise, whether in the general or the consulting field, in fact it means being qualified to learn.

Mr. Philip Wiles: Orthopædics has grown to a major branch of surgery during my own professional life. It is true that the word orthopædics, and the idea behind it, originated 200 years ago, but its influence was negligible until the First World War. It was then that Robert Jones, stimulated by the many thousands of unnecessary war cripples to be seen on crutches and in bath chairs throughout the country, showed that those who devoted themselves to the repair of injury and disease of the locomotor system could attain results undreamed by other surgeons. Their achievement was recognized after the war by the appointment of Orthopædic Surgeons to the major Teaching Hospitals. They set to work and passed their skill on to others with such effect that, by the time of the Second World War, there

were enough trained surgeons to deal with the casualties, both service and civilian. Since then there has been a snowball growth; and the British Orthopædic Association, which had perhaps 70 members when I joined it in 1931, now numbers more than 500.

It is obvious that the conditions now treated by orthopædic surgeons existed before the specialty developed, although the volume of work has increased by reason of the destructive nature of modern machines. Patients suffering from these conditions were formerly in the care of the general surgeons of the day who naturally taught the student about them. But the general surgeon is no longer responsible for these patients and therefore the duty of teaching the student has devolved upon the orthopædic surgeon. There can be no doubt about that. What we are concerned with here is the magnitude of the subject, its importance to the student, and the way in which the orthopædic surgeon is fulfilling his obligation as a teacher.

The magnitude of the problem can be shown by figures from my own hospital, The Middlesex, where we are fortunate enough to have a statistically minded records department. The number of patients for whom the two orthopædic surgeons are responsible is greater than that of all the four general surgical firms added together. Since nearly all patients attending the hospital are referred by general practitioners, the figures must give some indication as to the relative volume of orthopædic work in general practice. The bulk of the patients seen by orthopædic surgeons require non-operative treatment, and I am convinced that a large number could properly be advised by the general practitioner, if only he had been adequately taught as a student. In my own practice about 1 patient out of 8 requires operative treatment. I have no corresponding figures for general surgical practice, but it is probable that more than half require operation.

Orthopædic surgeons must teach the student to weigh the problems with which he is confronted in terms of human behaviour. We have to consider whether a physical defect in a child is likely to prove such a handicap in later life that drastic treatment is justifiable whilst he is young, or if it could be that the treatment would be a greater evil than the defect. And we must consider, when advising some major operative procedure for the relief of pain or for the restoration of function, whether the result is likely to be such that it is worth that patient's while to submit himself to operation. We have first of all to assess the benefit the patient may expect to receive from the operation provided it meets with average success. Can it be relied upon to relieve the pain? What will be the function afterwards, and will this satisfy the needs of that patient? Against the chances of relief we have to set the risks of the operation, and the cost to the patient. Every operation carries a risk. Even an operation for bunions has a certain mortality; and a number, for one reason or another, give a poor result. Every operation is time-consuming for the patient—some may mean as much as three or even six months away from work. Sometimes this is worth while and sometimes it is not. The answer is not easy and a decision can only be made after careful assessment of both the physical and psychological environment of the patient.

The larger part of the work of the orthopædic surgeon is undramatic—sprains, fractures of fingers and toes, infections of the fingers, and so on. It is rather a dull, routine job and therefore in the past it has been neglected. There used to be but little teaching on the subject; indeed the surgeon often had little personal knowledge on which to base his teaching. The work therefore fell to the lot of untrained doctors and casualty officers each of whom had to learn it afresh, and by himself. The consequent cost in morbidity, in patients' time and in the waste of man-power to industry was quite fantastic. A whitlow might mean a longer period of sickness than an acute appendix. The care of these patients in many places has been taken under the wing of the already overworked orthopædic surgeon because he is trained to regard the restoration of function as of first importance. We accepted the extra work because we could not stand by and see the job badly done. But it is not really specialist work, and it would not be, if the student were properly taught.

Much of the treatment prescribed by orthopædic surgeons is carried out by the physiotherapist. The general practitioner should be dealing with many of the patients himself and therefore he should have a working knowledge of the techniques of physiotherapy. He should certainly be competent to perform most manipulations himself. He must know what forms of heat are of value in different circumstances. He must understand the nature of postural defects in children. Above all, there must be physiotherapists available to help him. If the general practitioner is to be more than a sorting agent, he must treat ordinary complaints himself. The surgeon can be available for consultation if necessary, but at present the patient comes not only for consultation, but also for treatment, and he remains in the care of the surgeon.

I want to finish with a word about the other questions I posed. Is the orthopædist now fulfilling his responsibility as a teacher properly? The answer to this question is "No", the chief reason being that the student is stimulated to learn only about major orthopædic problems, and not at all about minor ones. The latter will bulk large in his future practice, but they have no place in his qualifying examinations.

Serious attention must be given some time soon to the teaching of undergraduate students not only in orthopædics, but in surgery as a whole, including all its specialized branches. Surgical teaching is not at present well balanced, and, in my opinion, too much emphasis is placed on the less common

conditions. Of course the student must learn to recognize the acute diseases of the abdomen and elsewhere that call for urgent treatment. And he must learn to recognize the major disorders that have a more chronic course. But above all he must learn to recognize when the patient is ill, and which are the deviations from normal that require investigation. The time spent on the details of diagnosis and treatment should be chiefly in respect of those diseases and those injuries which could, and should, be treated by the general practitioner.

It is going to be very difficult to restore a proper balance in teaching whilst the present arrangements exist in Teaching Hospitals. The general surgeon no longer has the clinical material on which to teach his students about *all* surgical problems. Moreover many general surgeons, for example those who have specialized in diseases of the genito-urinary system, or of the thyroid, are more specialized than the orthopædic surgeon. The time is approaching when such surgeons will no longer be regarded as being particularly suitable for the primary teaching of undergraduates, and this will be placed in the hands of those surgeons most fitted to undertake it. Who this may be will vary from hospital to hospital; those individual surgeons who are thought to be the best teachers should be given the responsibility of teaching regardless of whether their chief interest is in the treatment of diseases of the lower bowel or of osteoarthritis of the hip.

Summary

(1) "Orthopædic" complaints constitute about one-quarter of all surgical cases in general practice.

(2) The general practitioner should have the competence and the facilities to treat many of these complaints.

(3) It is the duty of the undergraduate schools to ensure that the general practitioner has the necessary competence.

Mr. P. N. Cutner: I believe that if the basic principles of manipulative treatment were taught to students, particularly during the course in surgical and applied anatomy, it would reveal those who have, lying latent, the art of joint manipulation and this talent could be developed during the clinical years so that by the time they graduate they are at least conscious of their ability in this sphere.

Mr. R. H. Metcalfe stressed two points: First, the importance of medical students spending at least one week of their training as residents at a long-stay Orthopædic Hospital. Secondly, the importance of impressing upon students in orthopædic surgery the necessity of avoiding mistakes and the dangers of litigation. In this respect Mr. Metcalfe referred to the great difficulty at the present time of getting Housemen in the Casualty Department as it was obviously impossible to use pre-registration qualified men in such a department.

Mr. S. A. S. Malkin said that recently medical students from a London hospital, who had come to Nottingham for the purpose of doing their practical work in obstetrics, visited Harlow Wood Orthopædic Hospital. Some of them subsequently asked if they could come to the hospital for a week or so as residents to gain experience of the type of work done there. Arrangements were made for them to live at the hospital for short periods. They all seemed to feel that this had been well worth while and that they had seen types of patients and treatment for which otherwise they would have had to rely on their books.

As next to Harlow Wood there was a Training College for disabled people, the students also had the opportunity of seeing men who were seriously and permanently disabled, overcoming their disabilities and taking training in work in which they could compete on equal terms with those who were quite fit. This could really be regarded as a branch of social medicine.

The Chairman pointed out that at King's College Hospital the junior surgical dressers during their first six months' period of surgery were attached to the Orthopædic Department for two months and to the Urological Department for two months so that they gained an insight into these two special subjects during their early medical training. The experiment had, so far, worked very well and the arrangement was being continued. These same dressers returned to the Orthopædic Department in a senior capacity at a later stage of their training.

It had been found useful to engage local medical practitioners as Clinical Assistants both in the Orthopædic Department and that of Physical Medicine. This maintained a close liaison between the local doctors and the hospital departments.

Section of Radiology

President—J. BLAIR HARTLEY, M.D., F.F.R., D.M.R.E.

[*November* 20, 1953]

SOME TRENDS IN RADIOTHERAPY SHOWN AT THE SEVENTH INTERNATIONAL CONGRESS OF RADIOLOGY:

Dr. J. Boland and Dr. R. C. Tudway: *Developments in Technique and Treatment Policy.*

Professor R. McWhirter: *Presentation of Results.* (*Acta radiol., Stockh.*, in press.)

[*January* 15, 1954]

Cushing's Syndrome

By BASIL STRICKLAND, M.B., M.R.C.P., D.C.H., D.M.R.D.
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CUSHING'S syndrome is due to the excessive formation of glucocorticoids by the adrenal cortex or by a tumour of the adrenal cortex. At operation or autopsy the adrenals may appear perfectly normal, they may show bilateral enlargement from simple hyperplasia or a cortical tumour may be present. In the latter event the tumour is very often malignant and the remaining adrenal tissue atrophic.

A few cases of Cushing's syndrome have been associated with tumours of the ovary, the thymus or the pituitary gland; whether these tumours are primary or secondary phenomena has not been established, but in any event they are rare and one may say that, in the vast majority of cases, the cause of Cushing's syndrome lies within the adrenal cortex. Here it may be noted that every clinical manifestation of Cushing's syndrome can be reproduced by overdosage with cortisone or ACTH.

Hyalinization of the basophil cells of the pituitary gland occurs very commonly in Cushing's syndrome; these changes are now regarded as being merely secondary to the intrinsic abnormality of the adrenal gland and do not appear to be of primary importance. The excretion of corticoids in the urine is increased in all forms of the disease.

Clinically females are more often affected than males, usually between the ages of 15 and 40. The onset is insidious with the progressive deposition of fat on the face, neck and abdomen, with relative sparing of the arms and legs. Weakness and fatigue are common. There may be amenorrhœa in the female and impotence in the male. The skin becomes greasy and acne may develop on the face and spread to the shoulders and back, broad purple striæ may appear and hirsuties of moderate degree develop. The face becomes dusky and the body generally somewhat pigmented. Bruising may occur with unusual ease following only minor trauma. Glycosuria and hyperglycæmia are present in 50% of the cases, polycythæmia occurs less frequently. Hypertension is common. Mental depression, emotional lability or more severe psychoses are relatively frequent.

Radiographically two main features are to be found, these being osteoporosis and fractures.

Osteoporosis is described as being a constant finding in Cushing's syndrome; it is thought to be due to a simple decalcification of the skeleton, although Albright suggests that the cause is a deficient formation of bone matrix resulting from a deficiency of protein.

Fractures of the vertebral bodies are described as not infrequent but fractures elsewhere are rarely given more than a fleeting mention. The ribs are described by one authority as being atrophic in some cases, and another authority states that the bones may bend before breaking. We disagree with both these statements.

In the following five cases from the wards of St. Mary's Hospital we have found that fractures are a more common feature than osteoporosis and that they are more widespread in the skeleton than has formerly been stressed.

Case I.—J. P., female, aged 24. Three years' history of increasing obesity and the appearance of red striæ on chest, abdomen and arms. Recently the scalp hair has ceased to grow and facial hair has grown to excess. While playing with her child, and without any particular stress or trauma, she suddenly developed a pain in her left lower abdomen, an X-ray revealing a fracture of the pubic bone.

Examination showed a typical moon face with undue deposition of fat on the chest and abdomen, a moderate growth of facial hair and purple striæ on the flanks, back, shoulders and breasts. B.P. 220/160.

X-ray findings.—There was some osteoporosis of the bones of the pelvis and the trabecular pattern was coarser than usual. There were three fractures of the pubic bones (Fig. 1) involving the ascending and descending ramus on the right and the descending ramus on the left. The callus formation was well marked, and this we found to be a fairly constant feature of the fractures in Cushing's syndrome.

There was no definite osteoporosis of the vertebral column; an X-ray of the chest (Fig. 2), however, showed not only the expected cardiac enlargement, but also a fracture of every rib in the right hemithorax except the 1st, 2nd and 12th, and fractures of the 7th, 8th and 9th ribs on the left. The ribs were porotic and the callus formation exuberant.

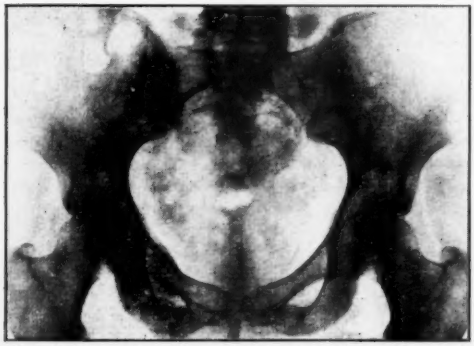

FIG. 1 (*Case I*).—Three fractures of the pubic rami. Two on the right and one on the left. Good callus formation.

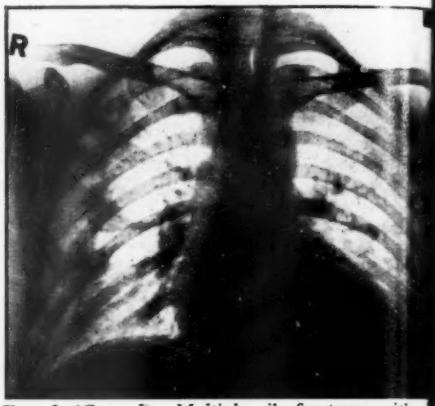

FIG. 2 (*Case I*).—Multiple rib fractures with well marked callus formation. Cardiac enlargement.

Case II.—M. E., female, aged 52 (a nurse). Two years ago while helping to lift a patient, she developed a sudden pain in the left groin, an X-ray showing a fracture through the neck of the left femur. During the past eighteen months increasing obesity of the face, neck, chest and abdomen. Increasing growth of dark facial hair, duskiness of the face, greasiness of the skin and acne. B.P. 180/100.

X-ray findings.—There was a fracture through the neck of the left femur (Fig. 3), undoubted osteoporosis of the spine with compression fractures of the 8th, 9th, 11th and 12th dorsal vertebræ and the 1st, 2nd, 4th and 5th lumbar vertebræ (Fig. 4). In the chest there were fractures of the 5th, 7th, 9th and 10th ribs on the left. The skull showed generalized osteoporosis, and the posterior clinoids appeared ghostlike but not eroded; they merely take part in the generalized osteoporosis of the skull as a whole. There was well-marked calcification of the vessels of the pelvis, a feature that is said to occur more frequently in Cushing's syndrome than in normal people. It was present in one other case.

FIG. 3 (*Case II*).—Fracture through neck of left femur, no osteoporosis at this stage.

Case III.—L. S., female, aged 23. Two-year history of a gradual increase in weight and the sudden onset of amenorrhœa. The face gradually became redder in colour and pains developed in the back. Examination showed a plethoric and rubicund appearance with marked obesity of the face, breasts and abdomen. Purple striæ of the abdomen, flanks, chest and arms, and a moderate growth of dark facial hair. B.P. 200/130.

X-ray findings.—There was moderate osteoporosis of the spinal column with collapse of the 11th dorsal and 1st lumbar vertebræ and early collapse of the 2nd and 3rd lumbar vertebræ (Fig. 5).

There was a fracture of the descending pubic ramus on the right, and fractures were present in the 12th rib on the left and the 11th rib on the right.

Case IV.—C. J., female, aged 32. Two-year history of gradually increasing obesity and, recently, amenorrhœa. Examination showed a moon face of dusky appearance with a minor degree of facial hirsuties. Disproportionate obesity of neck and abdomen. Scattered ecchymoses on arms and legs. Kyphosis and wide purple striæ of breasts and abdomen. B.P. 250/170.

X-ray findings.—In the chest, apart from the expected increase in the heart size, there were fractures of all ribs from the 5th to the 10th inclusive on the right and the 3rd, 4th and 5th ribs on the left. These ribs were not porotic (Fig. 6).

In the pelvis yet again there was a fracture of the descending ramus of the left pubic bone (Fig. 7).

Case V.—M. K., female, aged 46. Ten years' history of gradually increasing hirsuties associated with progressive obesity. Examination showed obesity of the face and abdomen with a marked pad of fat over the lower cervical spine. Coarse dark hair was present on the face, chest, back and upper arms. Dusky redness of the face. Diffuse pigmentation of the body and ecchymoses on arms and legs. B.P. 160/95.

X-ray findings.—There was no osteoporosis, but fractures were present in the 9th rib on both sides. The cardiothoracic ratio was increased, and there was a fracture of the iliac crest on the left.

This is an example of a fairly advanced clinical case of Cushing's syndrome showing only minor X-ray changes.

FIG. 4 (*Case II*).—Eighteen months later. Osteoporosis has now developed. Multiple compression fractures of lower dorsal and lumbar vertebræ.

FIG. 5 (*Case III*).—Collapse of lower dorsal and upper lumbar vertebræ. Moderate osteoporosis.

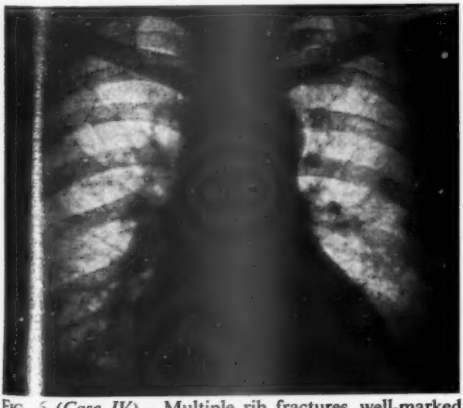

FIG. 6 (*Case IV*).—Multiple rib fractures, well-marked callus formation particularly on the right. Cardiac enlargement.

FIG. 7 (*Case IV*).—Fracture of descending pubic ramus on the left. Well-marked callus. No osteoporosis.

DISCUSSION

Of these 5 cases all showed fractures of the ribs, 3 had fractures of the pubic rami, 2 showed fractures of the vertebral bodies and 1 a fracture through the femoral neck.

The fractures, especially the rib fractures, must be looked for with considerable care. The whole skeleton should be radiographed, particularly the spine and the whole thoracic cage, with appropriate views for a clear delineation of the lower ribs. These rib fractures are often quite unexpected clinically even when multiple; thus 11 ribs were fractured in Case I, 4 in Case II, 2 in Case III, 9 in Case IV, and 2 in Case V, while only in Case I did they feature in the clinical history or examination, and only in this one case were the ribs undeniably porotic. All the fractures showed abundant callus formation. Here I would like to point out an apparent difference between Cushing's syndrome and the similar syndrome produced by cortisone. In Cushing's syndrome fractures appear to be very common and the healing of the fractures extremely good, whereas in cortisone over-dosage fractures have been reported but appear to be uncommon and, in animals at least, the healing of the fractures is much delayed. Of course the fact that healing of fractures is delayed in animals does not necessarily mean that it is also delayed in humans, but we think it of sufficient interest to follow further.

Two of the cases first presented as spontaneous fractures some time before a clinical diagnosis was made, one as a fractured femur, the other as a fractured pubis. Clearly this method of presentation must be borne in mind.

Although osteoporosis is regarded as a constant finding in Cushing's syndrome, its assessment is extremely difficult, for if the technical factors are altered only a little an apparent osteoporosis waxes and wanes in a most perplexing manner. Similarly if the patient rapidly becomes obese or equally rapidly loses weight after adrenalectomy, the assessment of radiographic osteoporosis becomes almost impossible, unless this is gross. The technical factors should be kept as constant as possible and one should always take control films of normal people of similar build, but even so the assessment of possible post-operative recalcification remains an arbitrary affair and often merely a matter of individual opinion. Certainly one must not be influenced by the clinical diagnosis and one must view the films as dispassionately as possible.

In our series, osteoporosis was present with certainty in only two cases—there does not appear to be a constant relationship between radiographic osteoporosis and the number or type of fractures. For example, Case IV had a fracture of the pubic ramus and 9 fractured ribs and no osteoporosis was present. Similarly, in Case II, no osteoporosis was present when the spontaneous fracture of the femur occurred, although this did develop subsequently.

Although it is generally agreed that the cellular changes in the pituitary gland are secondary to the adrenal abnormality, enlargement of the pituitary fossa is always looked for by the clinicians and practically never found. Of the cases in the literature quoted as showing enlargement of the pituitary fossa and erosion of the posterior clinoids it would appear that some of these are not examples of Cushing's syndrome in the present accepted sense (although this is in a state of flux), but rather of the adrenogenital syndrome, while others have shown merely decalcification of the posterior clinoids. One apparently authentic case described by Forbes is of some interest, for two films of the pituitary fossa had been taken. The first showed no abnormality, the second showed undoubted erosion, but this latter film was taken ten months after a four weeks' course of deep X-ray therapy had been given to the pituitary gland and from a purely radiographic viewpoint it must be discounted. If enlargement does occur it must be unusual and in any case no comment concerning this finding should be made without good coned lateral films being available.

Although no cortical tumour was present in our series (3 of the 5 patients having been surgically explored), presacral pneumography together with excretion urography is a vital part of the examination of any case of Cushing's syndrome. It is clear from the literature that tumours of the adrenal are not uncommon in this condition, and if the radiologist can demonstrate the presence of such a tumour, not only does he help the surgeon in deciding which adrenal gland to attack first, but he may aid considerably in the prevention of metastases by ensuring the early removal of the cortical neoplasm. When the kidneys and adrenals are clearly delineated by the air and with the pyelography under way A.P. tomograms of the renal-adrenal regions may give a very clear picture of the underlying situation. Before embarking on elaborate contrast procedures every effort should be made to delineate the soft tissues in the region of the adrenal glands by plain films of high quality.

Finally, in Cushing's syndrome the heart is often enlarged, and this appears to be related directly to the duration and degree of the hypertension which is so commonly present.

In Cushing's syndrome then the radiologist will survey the whole skeleton for fractures and osteoporosis, he should be diligent in his search for the former and critical in his assessment of the latter. He will expect the heart to be enlarged and the pituitary fossa to be normal, and he will carry out presacral pneumography, pyelography and possibly tomography in an attempt to demonstrate an adrenal tumour.

Comment.—The small series here presented suggests that (*a*) in Cushing's syndrome rib fractures are more common than fractures of the vertebral bodies, and (*b*) fractures generally are a more constant finding than osteoporosis. (*c*) Fractures of the pubic rami may possibly be a more common

finding than previously supposed. (*d*) The number and degree of fractures may not be closely related to radiographic evidence of osteoporosis and (*e*) there may possibly be a difference in the skeletal changes resulting from cortisone overdosage and the changes seen in Cushing's syndrome as such.

I wish to thank Dr. Rohan Williams for his help and advice in the preparation of this short paper, and Professor G. Pickering, Professor C. G. Rob and Dr. Carmichael Young for permission to use their cases.

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POSTSCRIPT (March 29, 1954): Since this paper was written a further case of Cushing's syndrome has been admitted to St. Mary's.

A careful radiological survey of the skeleton revealed fractures of 5 ribs, 2 vertebræ and the descending pubic ramus on the left. The fractures of the ribs and pubis were unsuspected clinically and quite painless. The rib fractures could only be seen on the penetrated film of the upper abdomen, being completely masked in the routine film of the chest.

Bone Changes in Diabetes

[By WILLIAM A. COPLAND, M.B., Ch.B., D.M.R.D.
United Bristol Hospitals

INTRODUCTION

W. R. JORDAN, in 1936, first drew attention to the co-existence of Charcot joints with peripheral neuritis in diabetics and in 1942 Bailey and Root, two American authors, described 14 cases of diabetes in which there was painless destruction of the joints of the tarsus. They were of the opinion that the conditions were true neuropathies and independent of impaired blood supply. Since then there have been various reports of these so-called Charcot joints occurring in diabetics suffering from neuritis and there are now in the literature records of 68 cases of this condition.

The knee-joint was affected in 3 cases which were reported individually (de Takats, 1945; Shore, 1947; and Spear, 1947) and 6 cases have been described in which the ankle was affected. 4 of these were put on record by Folke Knuttson (1951) who considered the radiological pattern to be similar to that seen in the Charcot joint of syphilis and syringomyelia. The tarsus has been affected in 32 of the cases, and the metatarsals in 52.

PRESENT INVESTIGATION

This paper is concerned mainly with the changes which are seen in the metatarsals and phalanges of diabetics. A radiological investigation was carried out on patients from the diabetic clinic of the Bristol Royal Infirmary who had symptoms or signs referable to their feet. Patients were X-rayed if they had features of a diabetic neuritis—that is to say, increased or diminished sensation or absent tendon reflexes. Patients with gangrene, absent pulses, corns and ulcers on the feet were also X-rayed. Of 50 patients examined in this way 19 showed bone changes. All were elderly patients, the youngest being 53 and the oldest 74. As some 400 patients attended the clinic during this period this represents an incidence of almost 5%. Records of 13 more diabetic patients with changes in the bones of the feet were obtained from Southmead Hospital, Bristol.

The classical features of a Charcot joint were seen in none of the cases. An alternative explanation was therefore sought for the changes and it was found that all the patients suffered or had suffered from an inflammatory lesion near the site of the affected bone. In most cases this was in a perforating ulcer. In other cases, especially where the phalanges were involved, there was or had been a septic corn or diabetic cutaneous gangrene. In this latter condition infection is of paramount importance (Grunberg *et al.*, 1951).

The direct cause of these lesions is an inflammatory invasion. Fig. 1 shows the paths that the process may take. An acute or low-grade soft tissue infection begins near a bone often near the joint (Fig. 1A). The first sign that may be seen is osteoporosis. Soon a break occurs in the cortex (Fig. 1B) usually in the neck of the affected metatarsal or phalanx and an osteitis ensues (Fig. 1C).

The condition then follows one of two main courses. If healing occurs a periosteal reaction will be seen along the shaft and the affected bone may be repaired (Fig. 1D and 1E). An example of this course is shown in Fig. 2.

Usually, however, the head of the bone is gradually destroyed (Fig. 1F). The shaft is attacked next and its medulla destroyed, progressively. As this happens so the cortical walls of the shaft approximate giving what may be called the taper or pencil appearance (Fig. 1G) (Hodgson *et al.*, 1948). Fig. 3 is an example of this process.

The appearances vary according to the virulence of the infection and the patient's resistance.

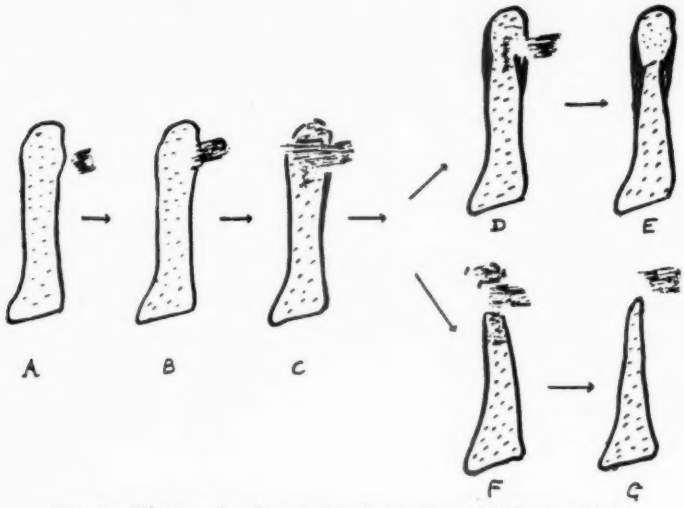

FIG. 1.—Diagram showing the possible courses of diabetic osteitis.

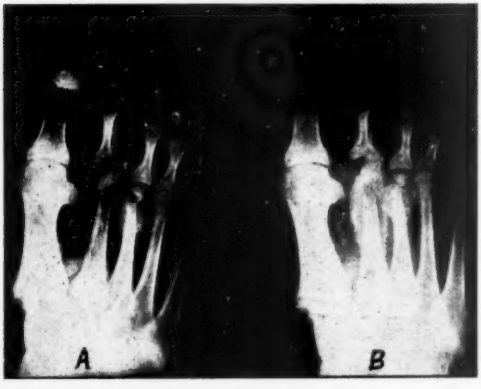

FIG. 2A and B.—The more acute variety of osteitis. The bones were normal when the underlying ulcer first developed. Radiographs taken subsequently show: A, Two months later. Partial destruction of the 2nd and 3rd metatarsal heads and medullæ with some periosteal new bone formation. B, Three months later. Repair of the affected shafts with marked periosteal new bone formation.

Furthermore the destructive inflammatory process may be arrested at any stage (Fig. 3c). This feature does not occur in neuropathic joints and is significant in differentiating the condition being described from such neuropathies. On the other hand destruction may advance to very gross disorganization. Fig. 4 is an example of this and illustrates a long-standing case with a 15-year history of ulcers of the soles and ankles. Repeated weight-bearing on the denervated foot does not help repair nor does the poor blood supply which appears to be a frequent accompaniment. Rundles (1945) and Martin (1952) have shown that, in fact, occlusive vascular disease is not a factor of primary importance. I consider that the destruction of the terminal phalanges seen in diabetic gangrene (Fig. 5) is due most commonly to a similar infective process.

Another feature of interest which was noted during the investigation was the formation of subperiosteal new bone along the shafts of the outer metatarsals in cases with a lesion on the medial side of the foot. This is seen in non-diabetics also and was thought to be associated with abnormal weight-bearing. Nor is the destructive bony process confined to diabetics. Identical appearances may be seen secondary to an infected corn or chronic ulcer on the skin of an otherwise normal patient.

Although there is no reason why a true Charcot joint should not develop in a diabetic with neuritis, it is considered that the vast majority of bone changes commonly seen in this condition, although influenced by poor blood supply, lack of sensation and possibly by the abnormal metabolism of diabetes are due to an inflammatory process. This explanation applies to a variety of other conditions affecting the extremities in which cutaneous lesions develop and are open to infection.

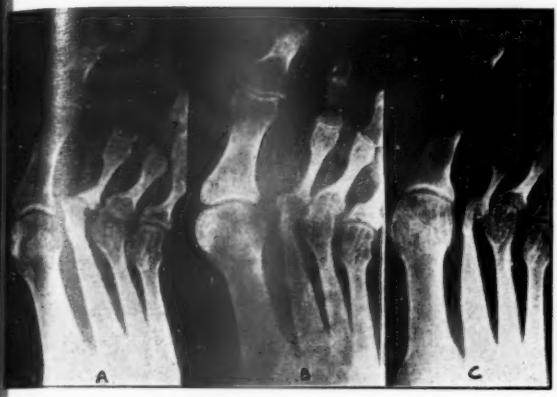

FIG. 3.—Chronic low-grade osteitis showing progressive tapering of the shaft. Radiographs taken in 1949, 1950 and 1953 of a patient who developed a perforating ulcer below the 2nd metatarsal head in 1949. A new cortex is forming round the distal end of the metatarsal in the latest film.

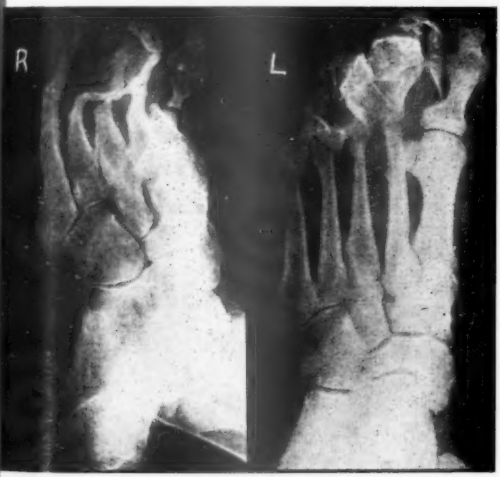

FIG. 4.—A long-standing case with a history of ulcers on the soles and ankles for fifteen years and suffering at present from an ulcer below the 2nd right metatarsal with periosteal new bone formation. Other metatarsals and phalanges and the ankles show the end-result of old low-grade inflammatory osteitis

FIG. 5.—Osteitis due to a perforating ulcer below right great toe. Infected blister two years previously on the left great toe which shows tapering of the terminal phalanx due to partial destruction of the tuft.

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Enuresis in Children

The Value of Radiological Investigation

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THE word enuresis is used to signify a state in which normal micturition occurs without the patient volition. It is a symptom, not a disease, and is not synonymous with incontinence of urine.

The enuresis which causes a parent to bring a child to hospital for treatment is invariably stated to be nocturnal but, in many cases, careful questioning elicits a story of actual diurnal enuresis or of late control of daytime micturition or daytime frequency.

In a recent two-year survey of urographic examinations carried out at the Bristol Children's Hospital it was noted that out of 276 children so examined between the ages of 2 and 15 years, 164 (59·4%) were investigated on account of enuresis. In this total there were 108 boys and 56 girls, and the incidence in this series is shown by age groups in Fig. 1. Gesell and Ilm (1946) state that there is considerable variation in night wetting, with girls achieving dryness considerably ahead of boys. The majority of children up to the age of 2 years wet the bed even although they are picked up at 10 p.m. by 2½ years, if the child is dry at 10 p.m. there is a fifty-fifty chance that it will remain dry, and by the age of 3 years the majority should be dry.

The history obtained from the parent may point to the underlying cause of enuresis. Two children in this series had never been known to be dry day or night and immediately the suspicion of an ectopic ureter presents itself—such proved to be the diagnosis in one case. The remaining children either had a history of occasional dry nights or had had a period of complete control of micturition and then relapsed. This relapse sometimes coincided with some emotional upset such as starting school, the birth of a younger child or coming into hospital for tonsillectomy, but no such psychological factor was apparent in many cases. Bad training or over-zealous training may be an important factor and several children were cured on being lifted regularly and taught clean habits.

INVESTIGATIONS

Each child had a complete clinical examination and about half had special tests which included intelligence tests, electro-encephalography, cystometrograms and blood urea estimations. 87 boys and 48 girls underwent cystoscopy. Chemical and bacteriological examination of the urine was carried out in every case and the results are shown in Table I.

TABLE I

	Clear Sterile urine	Trace of protein Few pus cells Sterile	Many pus cells Positive culture
Boys	100	5	3
Girls	45	4	7

7 of the 10 children who had a positive urine culture had a *B. coli* infection, one had a paracolon bacillus, one *B. proteus* and one boy had a mixed growth of *B. coli* and tubercle bacilli.

RADIOLOGICAL INVESTIGATIONS

Radiographic examination was carried out in every child, comprising a survey film to show the urinary tract and excretion urography. Following cystoscopy 1 boy and 6 girls had retrograde pyelography performed.

The preparation of the children was kept as simple as possible. They were encouraged to run about in their usual fashion up to the time of attending the X-ray department as it was found that this helped to minimize gas in the alimentary tract. Normal diet was allowed the day before the examination, all food and fluid being withheld for twelve hours only. The question of the use of aperients is a debatable one because many children who have regular daily bowel action will not require one, but children who were in the habit of having an aperient were given their usual dose. If the colon and rectum were seen to be loaded on the survey film, the use of a glycerin suppository frequently cleared the field and the examination was continued about one hour later.

Diodone was the opaque medium used in this series and it was given by intravenous injection except in 4 cases to whom it was given by subcutaneous injection with Hyalase. 35% Diodone was given up to the age of 8–9 years, and 50% Diodone over that age, allowance being made for very small or very large children. The dosage was based principally on age. For each year of life 2 c.c. of 35% Diodone was given or 1 c.c. of 50% Diodone.

Radiographs were taken at five, fifteen and thirty minutes after intravenous injection, and ten, twenty, thirty and forty-five minutes after subcutaneous injection, further films being taken later if required. When the bladder had been satisfactorily outlined, the child was asked to micturate and a further film was taken to visualize the amount of residual urine. With co-operative children films were taken during micturition to show the urethra but so far the information gained from these films has not been helpful.

Radiological findings.—The results of the urographic examination of the children in this series were as follows:

TABLE II

	Boys	Girls	Total
Normal excretion urography	60	28	88
Developmental anomalies	15	10	25
Trabeculation of the bladder	22	11	33
Significant residual urine	14	9	23
Other lesions	2	1	3

A few children had more than one lesion noted but of the total, 54 children (33%) had a significant lesion.

(*a*) *Developmental anomalies.*—The developmental anomalies included a solitary right kidney, a horseshoe kidney, an ectopic left kidney lying partially over the left iliac crest, and several cases of duplex kidney with or without reduplication of the ureter. A duplex kidney with a double ureter may be a very important finding as the ureter from the upper calyces may have an ectopic opening outside the control of the urethral sphincters.

A girl, aged 4½ years, had never had a dry day or night and excretion urography revealed a duplex kidney in which one separate calyx was seen above a normal right pyelogram. The double ureter was not outlined but on the residual film a linear collection of opaque medium was seen below the bladder outline. On clinical examination, the ectopic opening of the second ureter was found on the right side of the external urethral meatus with evidence of ureteric peristalsis. Cystoscopy revealed a normal bladder. In this case the implantation of the second ureter into the bladder completely cured the dribbling.

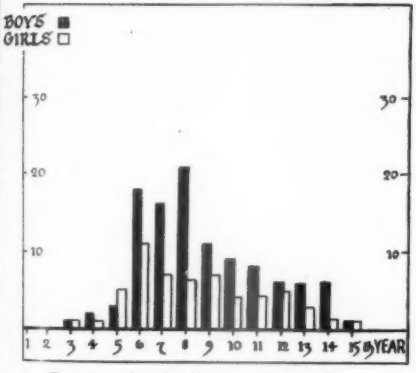

FIG. 1.—Age incidence of enuresis.

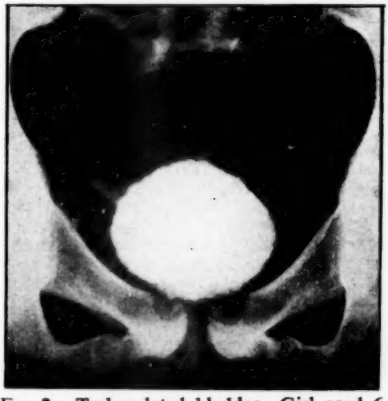

FIG. 2.—Trabeculated bladder. Girl aged 6 years. Bladder-neck hypertrophy.

(*b*) *Trabeculation of the bladder.*—The wavy irregular outline of the bladder seen on a radiograph is described as trabeculation (Fig. 2). It is taken as evidence of bladder disease and in this series it was associated with cystitis in 6 cases and with bladder-neck hypertrophy in 18 cases. No cause was found in the remaining 9 cases, 5 of whom were cystoscoped and the presence of trabeculation verified.

Bladder-neck hypertrophy creates a clinical picture comparable with prostatic obstruction in the adult and in children the presenting symptom frequently is enuresis. Radiologically, bladder-neck hypertrophy is recognized first by its effect on the bladder and later on the ureters and kidneys.

In order to overcome the obstruction, the bladder muscle hypertrophies so that the bladder wall is thickened; radiologically this is recognized by alterations in the cystogram appearances. The bladder may be contracted and spherical and may have a trabeculated outline. The trabeculation is due to hypertrophied intertwining muscle bands arranged in coarse bundles with evagination of the vesical mucous membrane between them. If the hypertrophy is untreated, at a later stage these small

evaginated pockets become larger when the bladder is described as having a sacculated ou ine an finally true diverticula are present (Fig. 3).

(*c*) *Residual urine.*—Under the age of 5 years, little importance can be attached to the ar ount o residual urine. Over this age after two attempts at micturition few normal children have mo than a trace of urine left in the bladder, therefore increasing importance can be afforded to the pre ence o residual urine. It was the only abnormal feature in 18 children of this series and in 10 of these i was associated with bladder-neck hypertrophy (Fig. 4).

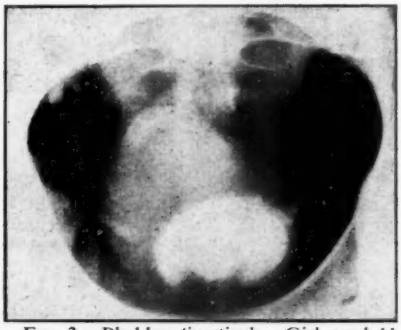

FIG. 3.—Bladder diverticula. Girl aged 11 years. Bilateral hydronephrosis. Bladder-neck obstruction.

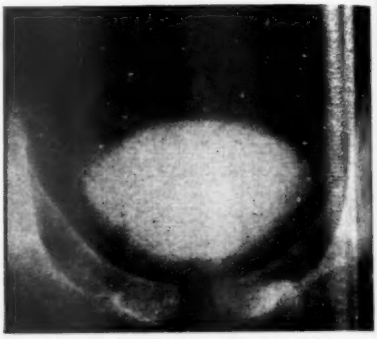

FIG. 4.—Residual urine. Boy aged 8 years. Bladder-neck hypertrophy.

In this series of enuretics 44 children were found at cystoscopy to have a significant degree o bladder-neck hypertrophy, 10 being severe enough to require transurethral resection to relieve obstruction. There were abnormal urography signs in 28 of these as shown in Table III.

TABLE III.—PROVEN CASES OF BLADDER-NECK HYPERTROPHY

	Boys	Girls
Normal urography	10 (2 T.U.R.)	6 (2 T.U.R.)
Bladder trabeculation	12 (3 T.U.R.)	6 (3 T.U.R.)
Residual urine	6	4

(*d*) *Other lesions.*—The remaining 3 children all had more severe renal lesions demonstrated by excretion urography.

The first, a boy of 6½ years, had only had an occasionally dry night throughout his life; only one of many urine specimens contained a few pus cells, cystoscopy was reported as being entirely normal but excretion urography revealed a unilateral hydronephrosis and a ureterocele.

The second case, a boy of 12 years, had suddenly developed nocturnal enuresis six months previously. Only after leading questions were put to him would the boy admit to daytime frequency and dysuria. Excretion urography in this case revealed a hydronephrotic right kidney, delayed excretion by the left kidney with opaque medium outside the calyces, a dilated straight left ureter and a small trabeculated bladder. The diagnosis of tuberculosis was confirmed when tubercle bacilli were cultured from his urine and at operation a tuberculous abscess was found in the left kidney with tuberculous infiltration of the left ureter.

The third case, a girl aged 8 years 9 months, had never had a dry night throughout her life and had marked frequency of micturition in the day. She had been treated by her own doctor on several occasions for urinary infections. The first specimen of urine examined was clear and sterile on culture, but a later specimen was found to contain many pus cells and *B. coli* were cultured. At cystoscopy the left ureteric orifice was reddened and œdematous and a specimen of urine from the left kidney contained pus cells. Excretion urography revealed distortion of the calyceal pattern of the left kidney and blunting of the calyces. The distance from the tip of the pyramid to the edge of the renal outline was reduced, i.e. the actual renal substance was diminished. This is taken as the radiological picture of chronic pyelonephritis, and this was regarded as a case of chronic pyelonephritis (with recurrent cystitis) causing enuresis.

CONCLUSION

Excretion urography plays an important part in the investigation of enuresis. From this series it appears that:

(i) 70–75% of the cases will probably be normal radiologically.

(ii) 20–25% will probably have bladder-neck hypertrophy which will be suggested or shown radiologically in the majority of cases. When present in a more severe degree its effect both on the anatomy and physiology of the urinary tract will be demonstrated and this will help the clinician in his assessment for treatment.

(iii) In a few patients (1–2%) the enuresis may bring to light other unsuspected conditions such as tuberculosis, hydronephrosis, or chronic pyelonephritis.

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Section of Epidemiology and Preventive Medicine

President—A. BRADFORD HILL, C.B.E., D.Sc.

[*January* 15, 1954]

DISCUSSION ON COMBINED IMMUNIZATION

Dr. H. J. Parish: *Combined Prophylactics*

Combined prophylactics reduce the number of injections necessary for immunization. When such mixtures are properly prepared and used, there should be no loss in antigenic efficiency. At least 14 double, triple and quadruple preparations for combating 10 infections have been studied by different workers (slide shown).

Diphtheria.—In England and Wales in 1952, the notifications (corrected) were 376, and the deaths only 32 (Ministry of Health: Annual Report). Primary immunizations numbered 561,858, and reinforcing injections 567,027. There was a wide variation in the percentage of children immunized in different localities, and the immunity state of our population is often disconcertingly low. The total percentage of children under 5 years immunized against diphtheria in the L.C.C. area was only 50 in 1952 (*see Brit. med. J.*, 1954, i, 21). Barr *et al.* (1951) found that 30 to 59% of samples of cord blood examined in 10 of 15 districts in the British Isles contained no detectable antitoxin. Complacency is unwarranted.

Whooping-cough.—The WHO (1952) stated that 95% of the world population are attacked by whooping-cough at some time or other. In this country, the deaths are diminishing, the official figure in 1952 being only 184, a record low level. But there is still much permanent lung damage (atelectasis and bronchiectasis) from the infection. Chloramphenicol and other antibiotics are rather uncertain in treatment, mainly because they are not used early enough; as recently recommended, chloramphenicol might be given as a prophylactic to close contacts. The Report of the Medical Research Council (1951) showed that prophylactic vaccination can be effective; further work is in progress, and the demand for active immunization is increasing. The Kendrick mouse intracerebral test is being used as the method of assay of vaccines before issue.

Tetanus.—In World War II, the American Army had only 0·44 cases of tetanus per 100,000 wounded. Amongst 10,700,000 men in the armed forces there were only 11 cases, with 4 deaths. As antitoxic serum was not used prophylactically, these low figures can be ascribed to the use of tetanus toxoid. The figures of the British Army provide collateral evidence of the value of specific measures of control.[1]

[1] Although it has received scanty recognition, the prevention of tetanus by tetanus toxoid was a major medical triumph of the Second World War.

M.

Chemotherapy is ineffective against tetanus toxin, as it is against diphtheria toxin. In England and Wales, there are approximately 200 cases of tetanus (40% fatal) per annum. A considerable proportion of the population receive antitoxin prophylactically. Active immunization with toxoid could replace much passive immunization with antitoxin, provided the method were extensively used and records were accurate and readily accessible. There is a good case for combined prophylaxis.

Gas gangrene.—Active immunization of man is feasible, if required. Preliminary work with a combined tetanus and gas gangrene toxoid was carried out during World War II. It is now held that adequate surgical treatment, and penicillin given systemically in adequate doses for several days, will prevent gas gangrene.

Scarlet fever.—In 1952, there were 23 deaths from scarlet fever and 41 from streptococcal sore throat in England and Wales. If infection should revert to a severe form, combined immunization, which incidentally was being employed in Aberdeen in 1929, could be revived.

Chemotherapy does not neutralize preformed toxin and therefore has certain limitations in treatment.

Enteric fevers.—T.A.B. vaccination has helped to reduce the incidence of typhoid and paratyphoid. Although chloramphenicol is effective in treatment, there is still a place for vaccination in prophylaxis. A combined T.A.B. vaccine with tetanus toxoid (T.A.B.T.) is of interest to the Medical Services of the armed forces of different countries; naturally, increasing emphasis is being placed on the tetanus constituent, because tetanus, once established, does not respond readily to any curative measure.

Cholera.—With regard to vaccination against cholera, Maddock (1948) found that, when there was equality of risk in selected groups, the attack rate in the "not inoculated" was 2·4 times that in the "inoculated" group. Rogers (1952) stated that vaccination is the most effective method of controlling cholera outbreaks.

Chemotherapy is unsatisfactory.

T.A.B. and cholera vaccine is available for use as a combined preparation.

Typhus fever.—While the use of chloramphenicol in treatment, and methods of attack on insect vectors, have done much to control typhus, a vaccine of typhus rickettsiæ is still considered of value in prophylaxis. French workers have added a formolized rickettsial vaccine to a combined T.A.B. diphtheria and tetanus prophylactic (T.A.B.D.T.R.) (Jude, 1950).

Yellow fever.—A combined yellow fever and smallpox vaccine has been used in mass immunization of native populations, and has the advantage of cheapness and convenience.

Finally, with reference to *post-inoculation poliomyelitis*, a closed season for inoculations might have to be considered during periods of exceptional prevalence of poliomyelitis. The avoidance of alum in diphtheria-pertussis and diphtheria-tetanus-pertussis prophylactics is also indicated on the available evidence.

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Miss Mollie Barr: *Some Immunological Considerations*

In the immunization of animals and man with a single prophylactic, the results depend mainly on dosage and spacing of injections. When combined prophylactics are used, results depend on dosage of two or more components, spacing of injections, the proportions of the various components and possibly the effect of one antigen on another. It is possible that some reaction may occur *in vitro* on mixing certain antigens, and also that irritation, produced after injection of one component of a combined prophylactic, may assist or hinder non-specifically the response to another.

There are, however, certain pitfalls in the immunization of persons and animals with two or more antigens given separately. Glenny *et al.* (1925) found that active precipitin formation interfered with both the primary and secondary responses of guinea-pigs to diphtheria toxoid. We have recently shown that an injection of diphtheria A.P.T. given to a diphtheria-immune horse at a time when vigorous production of tetanus antitoxin was occurring, evoked little response. The peak of the response was reached as late as seventy-one days after injection and the titre at this time was only 3·4 units/ml. Two earlier and one later injection, given during a resting time, stimulated normal secondary responses with peak values of 63, 70 and 67 units/ml. Thus in certain circumstances it may be unwise to give boosting doses of two separate antigens at close intervals. By using a combined prophylactic "double boosting" can be reduced to a single operation. There are, however, several factors to be considered both in the preparation and the use of combined prophylactics

As early as 1926, it was shown by Glenny and Waddington that in animals injected with a combined scarlet-fever-diphtheria prophylactic, an excess of scarlet fever toxin might depress the diphtheria response. In contrast to this, Greenberg and Fleming (1947) found that the addition of amounts of *H. pertussis* vaccine ranging from 20×10^9 to 160×10^9 organisms/ml. all improved the antigenic efficiency of diphtheria toxoid. It is possible that different combinations of antigens exert different mutual effects, and the absolute dosage of one and the same combined preparation can affect the response of animals to one component but not to the other.

We have carried out a number of experiments on the effect of dosage and of the relative proportions of the components of a combined prophylactic on the responses of animals to immunization. The guinea-pigs received two injections separated by an interval of twenty-eight days: blood samples were taken ten days after the second injection and were titrated for antitoxin content. In one experiment two prophylactics were used, both containing 60 Lf/ml. of a certain diphtheria toxoid and one containing 6 and the other 25 Lf/ml. of a fixed tetanus toxoid. The diphtheria antitoxin responses of guinea-pigs injected with the prophylactic containing 25 Lf of tetanus toxoid were significantly lower than those of the animals receiving the preparation containing only 6 Lf of tetanus toxoid per ml., although both groups of animals received the same dose of diphtheria toxoid. There are reports in the literature of results obtained in the immunization of babies with combined prophylactics containing about six times as much tetanus toxoid in relation to the diphtheria toxoid as the one used in our experiment. These reports show that unbalanced immunity resulted in the babies.

Other experiments showed that the tetanus antitoxin titres of guinea-pigs immunized with a given dosage of T.A.B.T. (tetanus toxoid and typhoid-paratyphoid A and B vaccine) were dependent on the T.A.B. content of the prophylactic. A preparation containing 5×10^8 *S. typhi* and $2{\cdot}5 \times 10^8$ each of *S. paratyphi* A and B produced good tetanus antitoxin titres in a group of guinea-pigs, the scatter being extremely small. When the vaccine content of the prophylactic was doubled, however, the scatter of tetanus antitoxin titres was considerable and some animals showed very poor responses. Thus, in the immunization of a large population with the first preparation, few very poor responders would be expected, but the second preparation might produce such considerable individual variation in response that a third dose would be necessary to ensure an adequate degree of immunity in a high proportion of the population.

Interference, due to overloading a combined prophylactic with one component, can sometimes be overcome by giving very large doses. For example, at one level of dosage the diphtheria responses to a combined diphtheria-tetanus prophylactic were significantly lower when the tetanus toxoid content was 25 Lf/ml. than when it was 6 or 12 Lf/ml. When, however, the dosage of these same combined preparations was increased fourfold, there was no significant difference between the responses of the groups of animals. This is shown in Table I and it is interesting to note that the

TABLE I.—EFFECT ON DIPHTHERIA RESPONSE OF DOSAGE OF COMBINED PROPHYLACTIC CONTAINING 60 LF OF DIPHTHERIA TOXOID PER ML., AND VARYING AMOUNTS OF TETANUS TOXOID

	Tet. toxoid		No. of guinea-pigs with diph A.T. titres							
	content	Dose	>0·2	0·5	1·0	2·0	5·0	10	20	
Group	(Lf/ml.)	injected	<0·5	1·0	2·0	5·0	10	20	50	G. mean
1	6 or 12	0·005			4	20	12	5	2	4·87
2	25		4	6	8	11	2			1·50
3	6 or 12	0·02		1	0	10	16	8		6·16
4	25			1	1	7	5	1	3	5·55

Means of logs: Groups 1 and 2 t = 4·55 P = <0·001
Groups 3 and 4 t = 0·39 P = 0·70

means of the logarithms of groups 1, 3 and 4 titres are homogeneous, showing that, so long as the tetanus toxoid content of the prophylactic was low, no advantage was gained in increasing the dose: the smaller dose was in fact adequate so long as the diphtheria response was not interfered with. Adequate tetanus immunity was produced by the lower dose preparations, and thus the effect of using an unbalanced prophylactic may be to increase the cost of immunization, because larger dosage may be necessary to establish adequate immunity to both components.

The foregoing experiments provide examples of how the dosage of a combined preparation and the proportions of the components can affect the immunity produced.

There is a third factor which can affect very considerably the results of combined prophylaxis. This is pre-existing immunity, in a person or animal, to one component of the prophylactic. We have studied the effect of pre-existing immunity to diphtheria toxoid on the responses of animals to the tetanus component of combined diphtheria-tetanus prophylactics. Even when a preparation containing excess tetanus toxoid was used, pre-existing immunity to diphtheria toxoid caused interference with the tetanus response. Similar results were obtained in T.A.B.-immune guinea-pigs immunized with T.A.B.T.: the tetanus responses were lower and more scattered than those of normal animals immunized in the same way (Barr and Llewellyn-Jones, 1953*a*). Further experiments showed that the interference must have been brought about by the secondary response to the diphtheria toxoid or T.A.B. vaccine contained in the first dose of the combined prophylactic (Barr

and Llewellyn-Jones, 1953*b*). Interference with the development of potential immunity might have occurred through crowding-out of the immunity-producing mechanism by the speed of the secondary response. Alternatively, or in addition, the duration of activity in this secondary response might have crowded-out the response to the second injection of tetanus prophylactic. Later experiments, not yet published, suggest that interference may occur with both injections.

The idea that pre-existing immunity to one component might interfere with the response to another in a combined prophylactic arose from some results of combined active and passive immunization in man (*see* Barr and Llewellyn-Jones, 1953*b*).

We have recently been investigating the diphtheria and tetanus responses of young babies to immunization with a triple prophylactic. I am indebted to Mr. A. T. Glenny, F.R.S., for collaboration on the immunological side and to Dr. N. R. Butler of University College Hospital for the clinical work. This prophylactic contained, per ml., 60 Lf of highly purified diptheria toxoid, 12 Lf of highly purified tetanus toxoid (both with suitable excess) and 40×10^9 *H. pertussis*. Three doses, each 0·5 ml., were injected into babies, these being given at the ages of 6, 12 and 18 weeks. Blood samples were taken at the age of 6 months and titrated for diphtheria and tetanus antitoxins. Estimations of diphtheria antitoxin in cord blood had been made for all these babies. The tetanus antitoxin titres of 77 babies showed a fairly small scatter, 87% were 2 units/ml. or greater. Diphtheria antitoxin responses were satisfactory in all babies whose cord-blood titres had been 0·04 unit/ml. or less. Some interference from passively-conferred antitoxin occurred in groups with higher cord blood titres, but the results suggested that delayed responses might occur in many of these babies. It would appear that better results could be expected if the first dose of triple prophylactic were delayed until the age of 4 months, although our results suggest that only about 10% of the babies examined could be regarded as unsatisfactorily immunized without further injection by the procedure we used.

Another triple prophylactic has also been tried out. In this preparation the dosage of the components was the same as in the first prophylactic, but the toxoids were adsorbed on aluminium hydroxide. Again the responses of the babies to the tetanus toxoid were very satisfactory, and there appeared to be active production of diphtheria antitoxin in all babies, including those with cord-blood titres of 1–2 units/ml. The injections of this prophylactic were given at the ages of 1, 6 and 14 weeks, the blood samples being taken at 6 months. It is probable that the addition of aluminium hydroxide so increased the antigenic efficiency of the toxoids that the reduction in the effect of the first dose, in those babies with high cord-blood titres, would be of little moment. It is probable that sufficient potential immunity developed in all babies, from the first two injections, for a good response to be evoked from the third.

Certain arguments have been brought forward against starting diphtheria immunization in the first few weeks or months of life. It has long been thought that inherited passive immunity interfered with the development of active immunity. In recent years, however, it has been shown that active responses are only delayed, not entirely suppressed, and it is therefore probable that very few babies fail to develop active immunity from early injections.

In our own experience with babies given two injections of adsorbed diphtheria prophylactic, at the ages of 6 and 14 weeks, 49 whose cord-blood titres ranged from 0·04 to 0·5 unit/ml. all had antitoxin titres above the Schick level at the age of 12 months: the majority were above ten-fold Schick level. Of 14 babies with cord-blood titres over 1 unit/ml., 11 had antitoxin values above the Schick level at 12 months. There is thus some interference, but this is not serious.

We have assumed that these figures are representative and can be applied to a large population. We have titrated more than 3,900 samples of cord blood and acting on this assumption, estimate that 985 out of 1,000 of all babies would be Schick negative at 12 months, after two injections at the ages of 6–14 weeks: 800 of this 1,000 would be expected to have titres of at least ten times that required to render them just Schick negative.

It is sometimes argued that titres at the age of 5 years will be lower in babies immunized in the first few weeks of life than in those immunized during the second 6 months. The secondary response fall and subsequent levelling would occur long before the age of 5 years, so long as immunization was carried out before the age of 18 months. The Schick negative rate at 5 years would not be expected to give any idea of when immunization was done. Babies immunized very early might indeed be more highly immune than those immunized later, because we have evidence that a considerable amount of natural boosting (from infection) still occurs. Such natural infection is, of course, far more effective as a stimulus after immunization than before.

When combined immunizations are started very early in life, it would appear expedient to give a primary course of three injections followed by a boosting dose at the age of a year. This should overcome the effect of interference with one component, brought about by inherited passive immunity.

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Dr. J. Ungar: The subject of combined immunization undoubtedly raises a number of issues that are still controversial.

The question of primary interest is whether or not the procedure of combining antigens is to be recommended. Experiments performed by various workers, and our own experience with laboratory animals, indicate that the simultaneous administration of antigens is practicable and that, if certain conditions are observed, immunization is effective (Ungar, 1952*a*).

I have demonstrated at a previous meeting of this Society (Ungar, 1952*b*) that the addition of vaccines to diphtheria toxoid enhances its antigenicity (Table I).

TABLE I.—ANTITOXIN RESPONSE TO 2·5 Lf OF PURIFIED DIPHTHERIA TOXOID INJECTED TOGETHER WITH NATURAL PRODUCTS

Group No.	Substance injected with the diphtheria toxoid	No. guinea-pigs in group	Mean antitoxin level in serum (units/ml.)
1	1 ml. saline (control)	11	0·11
2	1 ml. *H. pertussis* suspension containing 2,000 × 10^6 cells	11	2·89
3	1 ml. *B. coli* suspensions*	12	1·45
4	1 ml. suspension of *yeast cells**	12	0·43
5	1 ml. *yeast cell extract*†	12	0·15
6	1 ml. *Tetanus toxoid*	12	0·22
7	1 ml. 6% *dextran* in saline	11	0·17

*Equivalent to 2,000 × 10^6 *H. pertussis* cells by opacity.
†Equivalent to 300,000 × 10^6 yeast cells.

In more recent experiments we have confirmed that the addition of tetanus toxoid to the combined diphtheria-pertussis prophylactic does not alter the effect of the vaccine on immunity to diphtheria; on the contrary, the combination results in a high degree of immunity against both diphtheria and tetanus, an experience that seems to be confirmed in children.

I should like to give some results of our studies of certain factors involved in combined immunization.

(1) There is a certain proportion between the two or three components of a combined vaccine above which there will be a relatively smaller increase in antibody titres for a given increase in the size of the dose; in other words we reach a point where the law of diminishing returns operates.

TABLE II.—ANTITOXIN RESPONSE IN GROUPS OF 12 GUINEA-PIGS AFTER IMMUNIZATION WITH DIPHTHERIA-PERTUSSIS-TETANUS PROPHYLACTIC

Results expressed in units/ml. of antitoxin.
H. pertussis in all three groups 20 × 10^9 orgs./ml.

		Diphtheria Geom. mean	No. of guinea-pigs	Tetanus
Group 1				
Diphtheria	25·0 Lf	0·39	6	>0·70
Tetanus	3·6 „		5	0·21–0·63
Group 2				
Diphtheria	50·0 Lf	0·53	7	>0·70
Tetanus	7·2 „		2	0·16–0·63
Group 3				
Diphtheria	12·5 Lf	0·35	6	>0·70
Tetanus	1·8 „		6	0·05–0·46

TABLE III.—DIPHTHERIA ANTITOXIN RESPONSES OBTAINED IN GUINEA-PIGS IMMUNIZED WITH DIPHTHERIA-PERTUSSIS VACCINE

Groups of guinea-pigs were immunized with 1 ml. of the vaccine injected subcutaneously on two occasions

Diphtheria toxoid 1 Lf + 2,000 × 10^6 *H. pertussis* orgs./ml.	Diphtheria toxoid 5 Lf + 2,000 × 10^6 *H. pertussis* orgs./ml.
Geometrical mean .. 2·50	2·71

By keeping the concentration of the three components at certain optimal proportions, which must obviously be found empirically, we shall avoid the danger of excess of one antigen over the other, with the resulting adverse effect on the level of antibodies in response to the lower-dose antigen (Glenny's "crowding out" effect).

(2) In our experiments on guinea-pigs we were able to confirm the observation, previously made in children, that the presence of antibodies in primarily immunized animals will result in a lower antibody response than in animals without antibodies in their blood.

TABLE IV.—DIPHTHERIA ANTITOXIN TITRATION RESULTS
(Mean antitoxin level in serum of 12 guinea-pigs in each group)

Five groups of 12 guinea-pigs (250 grammes weight) were injected subcutaneously in the right flank with 1 ml. of guinea-pig immune serum containing 16 units/ml. of diphtheria antitoxin. Animals in four of the groups were injected on the same day in the left flank with 1 ml. of either purified diphtheria toxoid, diphtheria A.P.T., diphtheria-pertussis prophylactic or pertussis vaccine, respectively. A second dose was given four weeks later to three of these groups, omitting the one that had had the pertussis vaccine. At intervals of one, eight, twenty-eight and forty-two days the guinea-pigs from each group were heart-bled and the serum was titrated for diphtheria toxin. Controls, without serum pre-treatment, were included.

Group	Treatment	Units/ml. antitoxin after (days) 1	8	28	42	Controls (without anti-toxin) After 42 days
1	Antitoxin only (16 units/g.p.)	0·61	0·10	0·02	0·02	—
2	Antitoxin + diphth. toxoid 2·5 Lf	0·61	0·10	0·04*	0·53	0·60
3	Antitoxin + diphth. alum. phosphate adsorbed 1 Lf	0·61	0·10	0·09*	0·26	2·12
4	Antitoxin + diphth.-pertussis prophylactic 2·5 Lf ..	0·61	0·10	0·09*	0·52	2·80
5	Antitoxin+ pertussis vaccine	0·61	0·10	0·02	0·02	—

*Animals in Groups 2, 3 and 4 received second injection immediately after twenty-eight days' bleeding.

We must, however, add that, despite the low antibody response after primary immunization *these animals obtain a sufficient degree of basic immunity, as can be judged by their response to the secondary stimulus.* Table V gives details of the experiment.

TABLE V.—DIPHTHERIA ANTITOXIN TITRATION RESULTS
(Mean antitoxin level in serum of 12 guinea-pigs in each group)

Four groups of 12 guinea-pigs were injected subcutaneously in the left flank with 1 ml. of homologous guinea-pig serum containing 20 units/ml. of diphtheria antitoxin. Three of the groups were injected in the right flank with 1 ml. of diphtheria or pertussis prophylactic and a second dose was given four weeks later. At intervals of four, six and twelve weeks the guinea-pigs were heart-bled and the serum was titrated for diphtheria antitoxin. At the end of the twelfth week the guinea-pigs were reinjected with the respective antigens, the animals being bled two weeks later and their sera titrated.

Group	4 weeks second dose	12 weeks booster dose	14 weeks
1 Antitoxin only	0·08	Not tested	<0·003
2 Antitoxin + diphth. toxoid 2·5 Lf	0·07	0·45*	2·8
3 Antitoxin + diphth. toxoid alum. phosphate adsorbed 1 Lf	0·12	0·38*	5·3
4 Antitoxin + diphth. pertussis prophylactic	0·09	0·59*	6·4

*Animals in Groups 2, 3 and 4 received a third dose as a booster injection immediately after the twelve weeks' bleeding.

We have therefore to conclude from these experiments that the primary stimulus induces a state of latent responsiveness (basic immunity) in these passively immunized animals, since a secondary stimulus (booster dose) injected eight weeks later causes a rapid and profuse outburst of antibodies in body fluids.

Lastly there is the problem of intervals between injections. Some of our observations confirm the opinion that adsorbed antigens are slow-acting and protracted antigenic stimuli.

TABLE VI.—TIME FACTOR BETWEEN IMMUNIZING AND CHALLENGE DOSES IN MICE TREATED WITH ALUM. PHOSPHATE ADSORBED PERTUSSIS VACCINE (A.P.W.) AND PLAIN SUSPENSIONS OF PERTUSSIS VACCINE

No. of mice	Type of vaccine and dose × 10^6	Survival after 14 days	Percentage of survivals	Interval dose challenge
15	500 Suspension	8/15	53	10 days
15	500 A.P.W.	15/15	100	3 weeks
15	80 Suspension	0	0	2 ,,
15	400 ,, ...	5	33	2 ,,
15	2,000 ,, ...	9	60	2 ,,
15	80 A.P.W.	11	73	5 ,,
15	400 ,, ...	9	60	5 ,,
15	2,000 ,, ...	15	100	5 ,,
15	Nil	0	0	Control

Clearly the intervals between injections can be considerably longer with antigens adsorbed on alumina (A.P.W.) than when plain suspensions are used.

These results seem also to indicate that the antigenic response to vaccines adsorbed on aluminium phosphate is more marked than it is to an equal amount of plain suspensions.

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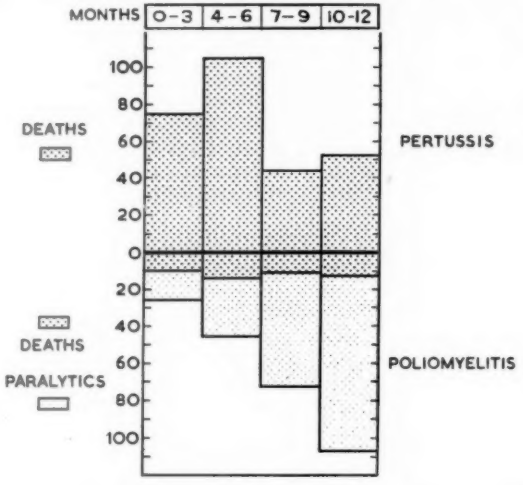
Dr. Neville R. Butler: *Clinical Aspect*

A scheme for combined prophylaxis against whooping-cough and diphtheria at present widely recommended is three equal doses of a suitably balanced combined prophylactic at monthly intervals, commencing between 4 and 6 months of age. Such a fluid prophylactic often contains 20,000 million *H. pertussis* organisms and 25 Lf purified diphtheria toxoid in the usual dose of 1 c.c. As inherited diphtheria antitoxin has fallen considerably by the fourth month of life, there is little need to consider passive interference. Therefore a plain suspension without mineral carrier should be effective, particularly as the antigenic effect of diphtheria fluid toxoid may be enhanced by the presence of pertussis organisms, in the absence of mineral carrier. But until the happy day when enough older children are immunized against pertussis to cut down the exposure rate among young infants, there may be no alternative to immunizing in the first three months of life, if the early pertussis mortality is to be diminished. Table I shows that this mortality is highest of all in the first few months of life. Thus, the earlier effective whooping-cough immunization is given the better; this also carries with it consideration of early diphtheria and tetanus immunity in combined prophylactics. The preliminary results of investigations on diphtheria-pertussis prophylactics given

TABLE I.—TABLE CONTRASTING TOTAL MORTALITY IN THE FIRST YEAR OF LIFE FROM PERTUSSIS AND POLIOMYELITIS, INCLUDING PARALYTIC POLIOMYELITIS SURVIVORS. REGISTRAR-GENERAL'S STATISTICS, ENGLAND AND WALES, 1950



in the early months of life are discussed later in this paper, the primary course being completed in most instances at the age of 3 months and a boost dose given at 1 year.

Any time-table for combined immunization must also make provision for separate smallpox vaccination and, if necessary, BCG. The latter should obviously be undertaken very soon after birth. To avoid risk of reactions, vaccination is not at present recommended at the same time as immunization. In 300 simultaneous smallpox vaccinations and combined immunizations at six weeks of age, we have noticed no increase in local or general reactions, nor any cases of vaccinia or encephalopathy, but the numbers are, of course, small. Any administrative scheme for combined immunization, be it early in infancy or later, must be applicable to large numbers of babies, in order to control spread of disease, as well as providing individual protection. Very early immunization would require special co-operation by general practitioners, midwives and staffs of maternity hospitals, but by the age of 6 weeks, the majority of initial welfare attendances under local authorities have

already taken place. Early immunization allows for an early boosting dose, perhaps between 1 and 2 years of age, but now conveniently done on school entry at the age of 5 years.

Reactions.—The next clinical considerations are local, general and neurological reaction rates after combined prophylactics. Table II illustrates the reaction rates after combined prophylactics given deep subcutaneously in the deltoid region, in the first month of life and between 1 month and 1 year. The term local reaction signifies a swelling or induration lasting over twenty-four hours,

TABLE II.—PERCENTAGE REACTIONS AFTER COMBINED PROPHYLACTICS
(DEEP SUBCUTANEOUS, DELTOID)

	FLUID				ADSORBED			
INJECTIONS		REACTION RATE			INJ.	REACTION RATE		
AGE	TOTAL	GEN.	LOCAL	ABSCESS	TOTAL	GEN.	LOCAL	ABSCESS
<4 WEEKS	200	1·0	3·0	0·5	170	1·2	27·7	7·6
>4 WEEKS	426	2·3	2·6	0	214	4·2	8·0	3·7

short of abscess formation. The term general reaction signifies a constitutional disturbance lasting over twenty-four hours and associated with either (*a*) fever, with or without irritability and crying, or (*b*) refusal of feeds, with or without diarrhœa and vomiting. The term abscess signifies an accumulation of sterile pus at the injection site which responded uneventfully to incision, but left a depressed scar. The usual policy was followed of postponing immunization in all babies with concurrent or recent pyrexia or severe illness and in any case of infantile eczema. It will be seen that the reaction rates following plain (fluid) combined prophylactics were negligible, both before and after 1 month of age. However, a high local reaction rate occurred as soon as a mineral carrier was added, adsorbed prophylactics giving an abscess rate of 7·6% under 1 month and 3·7% over 1 month of age. These high reaction rates might be lessened by deep intramuscular injections, although some believe the poliomyelitis danger to be greater.

Poliomyelitis.—Although the total injections (2,500) were small, no poliomyelitis occurred, in spite of continuing immunization with fluid combined prophylactics throughout 1953. WHO (1953) recommend postponing immunization only in major poliomyelitis epidemics, particularly as such postponement may be dangerous to immunization campaigns.

In view of a possible relationship between muscle trauma and poliomyelitis, after immunization, it would appear best to use non-irritant prophylactics such as plain fluid suspensions given subcutaneously at an age when poliomyelitis is least common.

Table I compares the whooping-cough mortality with the poliomyelitis mortality and paralytic notifications under 1 year of age in 1950, an epidemic poliomyelitis year. Allowing for the fact that less than one-sixth of childhood poliomyelitis cases have been shown to bear a significant relationship to previous injection (Geffen, 1950) the danger from whooping-cough is far greater than that from post-immunization poliomyelitis in the first year of life. It is also apparent that the death-rate from whooping cough is greater in the first 6 months of life and from poliomyelitis in the second 6 months of life, a point in favour of early immunization, while the boosting dose can be given as a fluid prophylactic at a time when poliomyelitis is not prevalent.

Results of trial.—At the L.C.C. Child Welfare Clinic of U.C.H. Medical School an attempt is being made to answer the following problems. Firstly, is whooping-cough protection after combined prophylaxis as effective as when the same prophylactic is given separately? Secondly, are combined diphtheria-pertussis prophylactics effective if given in the first few months of life, particularly with regard to whooping-cough immunity before 1 year and diphtheria immunity after 1 year, when these are respectively most needed? About 700 babies have been injected at approximately 1, 6 and 14 weeks of age with suspended and adsorbed pertussis vaccines alone and in combination with fluid diphtheria toxoid. The majority of the immunized babies were given a boost dose, all the combined prophylactic group being reinjected at 12 months of age, while the separate pertussis

prophylactic group were reinjected between 9 and 15 months of age. The schemes followed for the injection of the babies are shown in Table III.

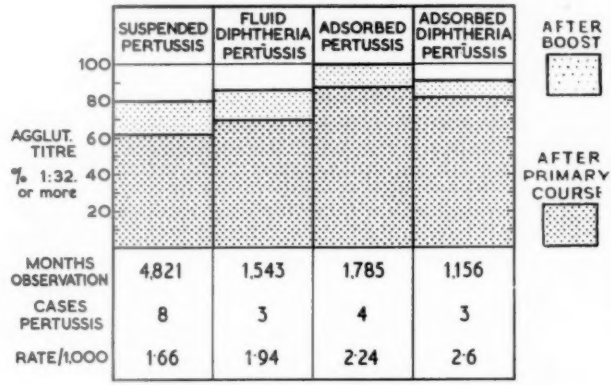
TABLE III.—PLAN OF IMMUNIZATION, SINGLE AND COMBINED PROPHYLACTICS

	Type of Prophylactic	Scheme	No. of babies	Age in Weeks 1	6	14	Boost	Strength of Prophylactic per c.c. Dip. Lf	Pert. Org.
Pertussis ..	Plain (fluid Suspension)	A	350	1·0 c.c.	1·0 c.c.	1·0 c.c.	1·0 c.c.	—	20×10^9
	Adsorbed ..	B	125	0·5 c.c.	0·5 c.c.	1·0 c.c.	1·0 c.c.	—	20×10^9
Dip-pertussis	Plain (fluid suspension)	C	55	0·5 c.c.	0·5 c.c.	1·0 c.c.	1·0 c.c.	25 Lf	20×10^9
		D	59	1·0 c.c.	1·0 c.c.	1·0 c.c.	1·0 c.c.	25 Lf	20×10^9
		E	24	1·0 c.c.	1·0 c.c.	1·0 c.c.	1·0 c.c.	50 Lf	20×10^9
	Adsorbed ..	F	78	0·5 c.c.	0·5 c.c.	1·0 c.c.	1·0 c.c. (plain)	25 Lf	20×10^9

Blood samples taken by jugular puncture three months after primary course and three months after boost, for diphtheria antitoxin and pertussis agglutinin titration.

Pertussis results.—A clinical follow-up is being carried out by questionnaire, with bacteriological confirmation wherever possible and the *H. pertussis* agglutinin levels have been estimated after primary immunization and boost. Table IV shows that the whooping-cough rate in immunized

TABLE IV.—PERTUSSIS CASE-RATE AND AGGLUTININ RESPONSE IN IMMUNIZED BABIES



M.R.C. TRIAL. 1951

VACCINATED	CONTROL
0·6 – 2·6	6·5 – 7·0

babies varied between 1·66 and 2·6 per 1,000 child-months' observation, being slightly less with plain (fluid) prophylactics than with adsorbed. This incidence, though numbers are not significant yet, falls within the same range as the rates of 0·6–2·64 per 1,000 months' observation in the group of babies immunized at over 6 months of age in the M.R.C. 1951 trial (*B.M.J.*, 1951). Although it must be remembered that the incidence of whooping-cough under 1 year is only two-thirds that in the second and third years, which formed the major part of the M.R.C. trial, these provisional results are encouraging. Table IV also shows that between 62% and 88% of the babies in the four groups showed *H. pertussis* agglutinin titres of 1 : 32 or more three months after primary immunization, with titres of 1 : 32 or more in 80%–100% three months after a boost injection. It must be stressed that these are not considered protective titres, at best indicating better immunity in those babies with higher titres. The correlation of pertussis laboratory tests with clinical pertussis incidence will be the subject of later work. The results also show that neither the pertussis case-rate nor the *H. pertussis* agglutinin levels were altered significantly when the *H. pertussis* vaccine was incorporated in a combined prophylactic.

Diphtheria results.—The diphtheria response after the same combined prophylactics was also investigated. 216 babies were immunized with combined diphtheria-pertussis prophylactics, plain and adsorbed, at approximately 1, 6 and 14 weeks of age, as in Table III. The strength of the diphtheria

component in each injection was not less than 12·5 or more than 50 Lf and the diphtheria antitoxin levels at the age of 1 year and 3 months later after a boost dose are shown in Table V. 25 babies

TABLE V.—DIPHTHERIA ANTITOXIN LEVELS BEFORE AND AFTER BOOST. PRIMARY IMMUNIZATION WITH COMBINED PROPHYLACTIC AT 1, 6 AND 14 WEEKS OF AGE

	Units diphtheria antitoxin	Plain (fluid suspension) Scheme		Adsorbed Scheme	
		C	D	E	F
Before boost	0–0·004	4	12	2	7
	0·01–0·1	44	42	18	49
	0·2–0·5	7	5	4	20
	1·0 and above	0	0	0	2
Three months after boost	0–0·004	0	1 (0·004)	0	0
	0·01–0·1	5	9	0	3
	0·2–0·5	17	25	7	10
	1·0 and above	26	16	14	56

Note.—A few babies failed to re-attend three months after boost.

(11·6%) of the total group showed diphtheria antitoxin titres at 1 year of age of 0·004 unit or less, i.e. at or below recognized Schick level, but after a boost dose all but 1 of 189 babies were above Schick level. As many as 56 out of 120 immunized primarily with plain (fluid) prophylactics and 56 out of 69 babies immunized primarily with adsorbed prophylactics had attained one unit or more of diphtheria antitoxin after boost. Thus, satisfactory diphtheria antitoxin titres were achieved by the time they were needed, after boost at 1 year of age.

Conclusion.—From these preliminary results there would appear to be a prima facie case for immunization of babies in the first three months of life with fluid combined diphtheria-pertussis prophylactics, provided a boosting dose is given at 1 year. There are certain administrative difficulties to be overcome, but the post-immunization poliomyelitis danger is less. Reactions are shown to be negligible in babies after plain (fluid) prophylactics, even in the very early weeks of life.

Acknowledgment.—The *H. pertussis* vaccines and the combined diphtheria-pertussis prophylactics were supplied for trial by Dr. J. Ungar, who carried out serological tests for *H. pertussis* responses. Miss M. Barr and Mr. A. T. Glenny were responsible for all the immunological work on the antitoxin responses.

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Section of Surgery

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[*January* 6, 1954]

Dupuytren's Contracture [*Abridged*]

By MICHAEL C. OLDFIELD, M.B.E., M.Ch.

INTRODUCTION

SIR ASTLEY COOPER described what is called "Dupuytren's Contracture" in these words in 1822:

"The fingers are sometimes contracted in a similar manner, by a chronic inflammation of the thecæ, and aponeurosis of the palm of the hand, from excessive action of the hand in the use of the hammer, the oar, ploughing, &c., &c. When the thecæ is contracted, nothing should be attempted for the patient's relief, as no operation or other means will succeed; but when the aponeurosis is the cause of the contraction, and the contracted band is narrow, it may be with advantage divided by a pointed bistory, introduced through a very small wound in the integument. The finger is then extended, and a splint is applied to preserve it in the straight position."

In 1831, Baron Guillaume Dupuytren confirmed by dissection that the contracture was due to shortening of the palmar fascia. A man, who had been under his observation for a long time, happened to die, and the Baron, by means unstated, possessed himself of the arm and dissected it. Afterwards he treated his patients by dividing the contracted bands of palmar fascia through multiple incisions, which he left open to granulate.

Anatomy of palmar fascia was described.

Function of palmar fascia.—At the crease lines, the palmar skin is firmly attached to the deep structures. This serves to preserve the concavity of the palm when grasping (Matthews, 1952). Without the palmar fascia, the skin would bulge forward and the grip would be lost.

Moreover, Dupuytren observed that the palmar fascia tends to bring the fingers to a state of demi-flexion, which is their state of repose; and it is nothing more than the excess of this function that occurs in the contracture called after him.

Pathology.—In Dupuytren's or Cooper's contracture, the palmar fascia becomes thickened, nodular and opaque. The fibres are shortened and lead to flexor contracture of the fingers. Histology reveals increased cellularity and many immature fibroblasts between which there are hæmosiderin deposits. The histological picture resembles that of a keloid or hypertrophic scar (Fig. 1).

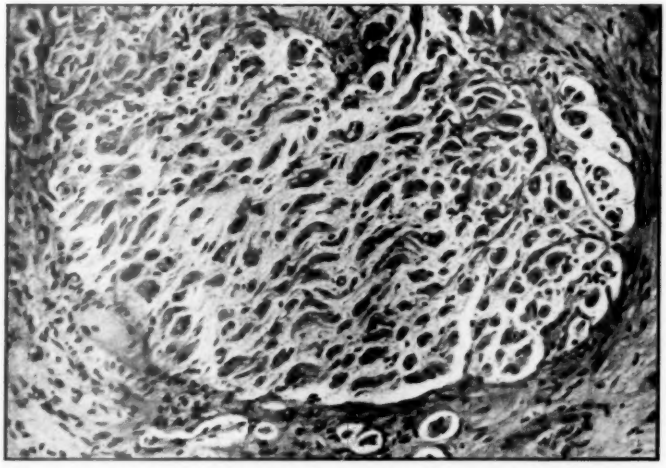

FIG. 1.—Photomicrograph × 98 showing histological appearance of palmar fascia in Dupuytren's contracture.

Ætiology.—Dupuytren's contracture occurs usually in elderly or middle-aged men. It does occur, however, less commonly in young men, but it is comparatively rare in women, being about ten times less common than in men. It is usually bilateral, but when unilateral, it is as equally common on the right side as on the left, although most people are right-handed.

There seems to be some hereditary predisposition in many patients, and a family history is obtained in about 10% of them. In certain families it is inherited through the males in each generation and identical contractures have also been observed in uni-ovular twins (Couch, 1938; Bergh, 1939).

Associated deformities.—(*a*) *Knuckle pads*: In some families, knuckle pads are inherited in some individuals, whilst Dupuytren's contracture of the hand or foot occurs in others (Fig. 2). About

FIG. 2.—Dupuytren's contracture of the sole of the foot.

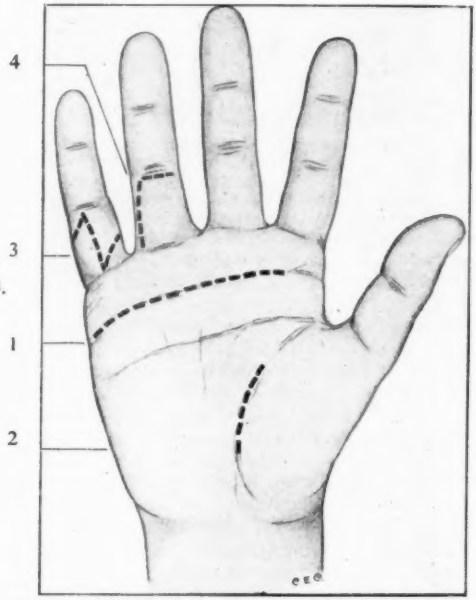

FIG. 3.

FIG. 3.—Incisions in palm, showing the classical transverse incision along the distal palmar crease line (1). The incision along the inner side of the thenar eminence which is useful on occasions (2). The "Z" incision (McIndoe) (3). Inverted "L" incision which can be used if there is no skin shortening (4).

one-tenth of the patients suffering from Dupuytren's contracture also have knuckle pads. Garrod, in 1893, first noticed the association of Dupuytren's contracture with knuckle pads. These occur in pairs over the back of the proximal interphalangeal joints of all fingers, except the thumb, and occasionally over the toes. They are similar histologically to the fibrous tissue which is present in the palmar fascia in Dupuytren's contracture. They cause slight disfigurement, but no appreciable disability.

(*b*) *Foot contracture*: When Dupuytren's contracture occurs in the foot it never causes flexor deformities of the toes. The patient complains of discomfort when walking due to a hard lump on the inner side of the sole: on examination, a hard nodule can be felt in the inner third of the plantar fascia. The histology is similar to that of the palm. Contracture of the plantar fascia may occur alone, but it is more often than not associated with knuckle pads or contracture of the palm.

CAUSE

The cause is unknown, but it seems that some people are born with a predisposition to it.

Theories of origin: Trauma, i.e. repeated irritation. Certain of Dupuytren's early patients seem to have made a great impression upon him. For instance there was a certain "cocher de fiacre" who had to ply his whip, which had a hard and heavy handle, almost unceasingly "pour hâter la lenteur de deux mauvais chevaux". A wine merchant complained that his palms were repeatedly bruised during the course of each day as he had to tap a large number of casks with a bradawl. Later Dupuytren noticed the contracture to be common also amongst masons and ploughmen. In other patients he said that he had not been able to find any cause for the malady, but concluded that it occurred most frequently in those who had been forced, when working, to use the palm of the hand as a "point d'appui". In Germany and other countries on the Continent, Dupuytren's contracture is considered an industrial

disease. In England, Sir Robert Jones (1912) stated in Court that the cause was probably a predisposition in an individual with palmar irritation as the exciting cause. Herzog in 1951 made an investigation upon 3,000 Yorkshire workmen and concluded that there was no evidence to show increased liability to Dupuytren's contracture in miners or steelworkers, as he had found it almost as often in clerks. He did not consider that claims for compensation could be supported. In America, Kanavel, Koch and Mason (1929) and Bunnell (1944), found the contracture more frequently in non-manual workers than manual workers. I found it present in non-manual workers twice as often as in manual workers. Skoog (1948) made histological studies in 29 of McIndoe's patients and concluded from these that there was histological evidence of injury to the fibres of the palmar fascia and considered that the changes in Dupuytren's contracture were analogous to those of a keloid or hypertrophic scar. He believed that this was due to repeated fracture of the collagen bundles caused by stretching and tearing over a prolonged period. He observed rich cellular connective tissue and fibrils which looked frayed and had a wavy structure, which is said to be characteristic of fracture of a collagen bundle. He also drew attention to the iron pigment in these cellular areas which seemed to indicate previous hæmorrhage and trauma.

Luminal therapy.—Lund (1941) found that the incidence of Dupuytren's contracture in an epileptic colony in Denmark was remarkably high. In comparison with a control series of 1,021 manual workmen in a brewery, Dupuytren's contracture was found to be four times more frequent amongst the epileptics. Also the age of onset seemed to be considerably lower than usual. Knuckle pads and plantar nodules were also more frequent in the epileptics. Lund suggested that it was possible that luminal therapy might be an ætiological factor. Skoog made a similar investigation upon 207 men in an epileptic home near Stockholm and found Dupuytren's contracture in 42% of them.

As hereditary defects are often multiple these facts may only be the manifestation in figures of a concentrated congenital taint in the colonies for epileptics, where accentuation of family defects could be expected. Only one of my patients, a woman, suffered from fits, but it was not certain that these were caused by epilepsy.

Clinical Course

In the hand, a nodule appears first in the palmar fascia beneath the distal palmar crease; soon the nodule becomes firmly adherent to the skin which is drawn into crescentic folds or dimpled into funnel-like depressions. Indurated plaques may occur later and spread across the palm. There may or may not be pain when grasping. Later flexor contracture occurs in the fingers distal to the nodule in the palm and progressive flexion takes place at the metacarpophalangeal and proximal interphalangeal joints. The distal interphalangeal joint is never flexed. Later several fingers may become permanently hooked into flexion and the patient may not be able to let go, when grasping the handle of a door or a strap in a tube-train or tramcar. Not only is he unable to grasp firmly, but he is unable to release his grasp quickly.

Progress is variable. In young patients flexor contracture may ensue rapidly within a few months of onset, whereas in old people contracture may progress slowly and extend over a period of twenty to thirty years.

Differential Diagnosis

When delivering a clinical lecture at the Charité Hospital in 1885, Professor Landouzy (1906) described a condition of permanent and irreducible flexor contracture of one or several fingers which develops gradually in young girls. It is usually bilateral and in most cases only the little finger is affected; but occasionally the ring and middle fingers are also involved. There is no flexor contracture at the metacarpophalangeal joints, but only at the interphalangeal. All the soft tissues on the flexor surface of the fingers are shortened. No nodules can be felt in the palmar fascia and the skin is not thickened or dimpled. The peripheral circulation of the fingers is sluggish; the fingers are thin and tapering, and the skin over them pink and shiny.

When Landouzy described this rather rare, but now well-recognized deformity, he called it "Campto dactylie": a name I dislike. I prefer the more correct name "Campylo-dactyly" derived from *καμπύλος* and *δάκτυλος* (bent finger).

At present no satisfactory local treatment is available, but it is possible that cervico-dorsal sympathectomy might be useful to improve the circulation and to halt the contracture. As I have only done this operation for one patient, I wish merely to suggest this treatment rather than to advise it.

Treatment

The standard treatment for Dupuytren's contracture is excision of the affected fascia by open operation, but this is not advisable in all patients.

(*a*) *Non-operative.*—If the patient has no flexor contracture and little disability, operation is unwise because the natural course of the disease is so variable. In some very old patients with finger contracture, but who have given up work, it may also be unwise to advise operation if the risks of anæsthesia are great.

Passive movements, exercises and other forms of physiotherapy are useless and may be harmful. Subcutaneous fasciotomy is unsatisfactory.

Vitamin-E therapy appears to be useless.

Radiotherapy.—Radiotherapy in the form of a radium mould or deep X-ray has been used at the Radiumhemmet in Stockholm for some years. Professor Sven Hultberg (1953), the director, has told me that he believes it to be useful in early cases to prevent further contracture. However, in old advanced cases where contracture is pronounced, he considers radiotherapy to be of no use. Slavina (1948) from Prague has described the use of radiotherapy in 107 patients with variable effects. Finney (1953) of St. Thomas's Hospital reported recently upon the treatment of 25 patients by application of a radium mould. A quarter of these made a full recovery, a quarter were partially improved, a quarter slightly improved and a quarter remained static. In this small series no patient was made worse and there was no report of any radionecrosis which would seem to be the great danger of this treatment.

Personally I think that radiotherapy is rational, but risky.

(*b*) *Operation.*

(1) *Hand.—Indications for operation*: Open operation for excision of the palmar fascia is indicated when flexor contracture is present and the history suggests fairly rapid progress. In bilateral cases, as in bilateral kidney lesions, it is probably wise to operate upon the least affected member first, as contracture here is likely to be more rapidly progressive: the results of operation are more satisfactory and likely to leave the patient with at least one naturally functioning hand.

The technique of operation was described (Fig. 3).

Alternative operations: (i) *Skin graft.*—If the skin is extensively involved or ulcerated it may be necessary, on rare occasions, to excise the damaged skin and replace the defect by a full-thickness free skin graft from the abdomen.

(ii) *Amputation of an irreparable finger.*—In late cases when the ligaments and tendons are shortened and the skin is defective, the results of conservative operation are unsatisfactory. Amputation of an irreparable finger, especially the fifth, may prove to be a wise decision. If the patient is old he need not be confined to bed for more than a few hours and he is likely to be in hospital for a few days rather than a few weeks. In Chitty's manœuvre the skin is filleted from the finger to be discarded and used to replace damaged skin in the palm.

Treatment of knuckle pads.—Knuckle pads, which are continuous with the extensor expansion and capsule of the proximal interphalangeal joints should rarely be excised as they cause but little disfigurement and rarely disability.

(2) *Foot.*—After exsanguination, a long curved incision is made along the inner border of the foot. The medial third of the plantar fascia is then excised.

Results

In the majority of early cases of hand deformity excellent results can be achieved if the skin is not extensively involved and the ligaments of the proximal interphalangeal joints are not shortened. In the late cases with severe contracture results are often disappointing. The results of operation upon the foot are usually excellent.

Conclusions

Dupuytren's contracture should be called "Cooper's Contracture". Its cause is unknown.
A family predisposition is often inherited.
Its origin is unlikely to be attributable to the patient's work.
It occurs usually in elderly and middle-aged men and is unusual in women of any age.
It is generally bilateral and often associated with knuckle pads; occasionally it is also associated with nodules in the plantar fascia.
The indications and technique of the modern operation for excision of the palmar fascia were described.
Radiotherapy may be useful before and after operation, as for keloid.
Vitamin-E treatment does not seem to be of any value.
In early cases with moderate contracture, results following open operation for excision of the palmar fascia are satisfactory.
In advanced cases when there is skin ulceration and shortening of ligaments at the proximal interphalangeal joints, amputation of the affected finger, especially if this is the fifth, may be preferable.
In the foot, excision of the inner third of the plantar fascia is followed by good results.
Knuckle pads are best left alone.

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Mr. Patrick Clarkson: The radical fasciectomy operation, so valuable for the younger age-groups, has serious limitations and dangers if used routinely for the elderly.

My own patients are generally elderly Army officers. These are very good material; fit, intelligent, co-operative, demanding a high result, and extremely prompt to report back.

The two chief difficulties in surgical treatment of Dupuytren's contracture are post-operative stiffness, whether or not associated with hæmatoma and necrosis, and recurrence. My view is that recurrence can be a lesser evil than severe post-operative stiffness. The radical fasciectomy operation with its dissection of the deeper extensions of the fascia into the palm gives the greatest freedom from recurrence; but the guarantee is not absolute as there are extrafascial sites of the disease which cannot be excised as a prophylactic routine. Nor does the radical operation include a routine prophylactic clearance of fascia from along every digit including the thumb. Recurrences are sometimes found in these sites.

In elderly patients, some hands have taken nearly a year to "ungum" completely after radical fasciectomy.

Dr. S. Bunnell, of San Francisco, confirmed my view that in the elderly and rheumatic a local excision of the affected fascia was preferable to the radical fasciectomy operation, because of the post-operative stiffness associated with deep and extensive dissections done in the latter. Recurrences after this limited operation, can be treated by a similar local relatively minor fasciectomy, with free graft replacement of skin when necessary. Mr. K. Starr, of Sydney, has reverted to Dupuytren's original procedure of fasciotomy, applying free pinch grafts when necessary to skin defects. My own practice is to reserve the radical procedure for patients generally under 50 without rheumatic or fibrositic tendencies, and to combine this with a Z plastic of the affected digits when necessary. I do not hesitate to amputate the little finger when the proximal interphalangeal joint is badly subluxated. I have had only one completely successful case of proximal interphalangeal arthroplasty, and I do not consider the chances of arthroplasty high enough to warrant retention of the fifth digit in most cases when the proximal interphalangeal joint is subluxated in acute flexion. In the older age-groups I do a limited removal of the affected fascia, and try to leave a bed on which a free skin graft can be applied, if the skin is heavily involved and has to be removed.

For the very elderly and rheumatic and those with gross deformity, I believe there is real value in fasciotomy combined, where necessary, with application of patches of thin, split skin. These take readily on such sites. This "straightening" procedure might, with advantage, be followed at a later date by a radical fasciectomy in patients to whom full function is particularly necessary and who are prepared to tolerate some months of relative stiffness.

Cortisone.—I have used cortisone for three years—100 mg. from the fifth to twenty-first day, plus, on occasions, 25 mg. a day for a further three weeks. I have not had any local complications; but there is certainly a risk of wound disruption. I have a firm impression that the patients treated with cortisone have been much more mobile than similar patients treated without the drug.

The natural history of the disease is extremely variable. At the moment it is virtually impossible to assess accurately the results of treatment from the point of view of recurrences because of this variability in natural history, and the difficulty of obtaining for comparison large enough groups of strictly comparable cases.

X-ray treatment.—The important objection to this method, especially in elderly patients, is that it must increase the chances of skin necrosis if a later operation has to be done. Nevertheless it can be of value, especially for young, tender nodules and early post-operative recurrences.

To recapitulate, my chief plea is for selection of the type of operation most suitable for the individual patient. This might be a radical fasciectomy, a local fasciectomy, or in cases of very gross deformity, and in the very elderly and rheumatic, a fasciotomy, with patch skin grafts when necessary.

Mr. D. N. Matthews: It is most important that an extension splint should be worn at night for three months after operation. This is advisable in cases in which full extension has been obtained at operation in order to prevent recurrence, and in those in which capsular shortening has prevented full extension in order to increase straightening gradually.

The drainage tube inserted at operation should be long enough to protrude through the bulky pressure dressing in the palm. It can then be withdrawn after forty-eight hours without disturbing the operation field. To minimize post-operative stiffness the patient should be encouraged to move the finger tips as much as the restrictive pressure dressing allows throughout the whole of the post-operative period.

The Treatment of Empyema Thoracis[1] [*Abridged*]

By A. L. D'ABREU, O.B.E., Ch.M., F.R.C.S.
Birmingham

THORACIC empyema complicating pneumonia no longer presents the classic pattern of former days. With acute pneumonia losing its virulence and being greatly modified by antibiotic and sulpha therapy, empyema development is unusual although transient opalescent effusions are not infrequent. During the five years ending in 1952, only 38 empyemata following or accompanying pneumonia have come under my own care, an experience of less than 8 a year (Table I).

TABLE I.—PNEUMONIA EMPYEMA 1948–1952

38 cases: Infants 8	Over one year 30		
Treatment: Aspiration 6	Rib resection and drainage 13		
Drainage 1	Decortication 17		
1 Death: Infant, died 2 hours after admission			

The history of thoracic empyema is studded with great names such as Hippocrates, Ambroïse Paré, John Hunter and Evarts Graham. The classical contributions of Graham following on the catastrophic story of empyema complicating the influenza pandemic at the end of the 1914–18 war are well known; the need to avoid an open pneumothorax in the presence of thin pus, usually streptococcal, with an associated pneumonia and a greatly depressed vital capacity was established. His objections were valid, scientific and life-saving at the time. As often, in the history of surgery, warfare alters ideas and conditions and the advent of efficient chemotherapy and antibiotics had an even greater influence. The rapid control of pleural infection by antibiotics and the availability of good anæsthesia with control of lung movements has largely removed the dangers of an adequate thoracotomy.

Colonel E. D. Churchill, consultant to the American Army in Italy during the 1939–45 war, asked the surgeons in that theatre if they were ignoring a principle of surgery or establishing a new one, when he observed them using a wide thoracotomy incision for the evacuation of traumatic empyema and decorticating the lung at the same time. Many such operations were performed throughout the world in the last war with highly satisfactory results and a mortality rate under 1%. Their great value was shown by the rapid re-expansion and return to function of the lung following a very short period of drainage.

Three principles underlie the treatment of thoracic empyema.—

I. The relief of respiratory obstruction.
II. The control of infection.
III. The restoration of function of the underlying lung and of the thoracic parietes.

The first two objects are achieved by the use of intelligent, thorough aspiration: but these, too, often leave a legacy of temporarily sterile masses of fibrin within the pleural cavity which coat the parietal and visceral pleura. This fibrin forms notably in pneumococcal infection but also in streptococcal ones treated by antibiotics. Much misunderstanding has dogged the brilliant achievements of penicillin in the treatment of pleural infection. It effectively sterilizes the infected contents but cannot prevent fibrin formation. If all the contents of an empyema can be evacuated by a regime of daily aspiration, conducted under constant radiological control, the results can be perfect.

In infants under the age of 1 this treatment holds the field; in 8 such patients drainage was employed in only 1 and the results, apart from 1 infant who died within two hours of admission, were clinically and radiologically perfect. Apart from empyema complicating staphylococcal septicæmia in infants this type of disease has lost its terrors and its previous high mortality rate. In adults penicillin-aspiration treatment is largely discredited because of a foolish persistence in attempts to aspirate that which will not be aspirated; nor in my experience have the lysing effects of streptokinase and streptodornase helped much in this problem. Unless rapid return of the pleural cavity to normal has been obtained, surgery is essential if the development of "penicillin empyema" is to be avoided. The influence of antibiotics, as in other areas of the body, has modified the normal process of suppuration but has not removed the need for surgical drainage.

Antibiotics and a good aspiration technique have rendered obsolete intercostal drainage as a measure to tide over a sick patient up to a state sufficiently stable to withstand rib resection. Surgery should be called for before complicated pockets of fibrin-lined pus have developed as simple rib resection may then suffice.

If the tube management is correct, chronic empyema will not develop; the essential demand is to maintain the tube in a correct site until there is no empyema cavity left. This is estimated chiefly by the use of radiology after the cavity has been outlined by Lipiodol (sinography); the need for mutilating thoracoplastic operations, etc., for the cure of chronic empyema should, by now, have disappeared.

[1]The paper was illustrated by 22 slides.

The present position.—Because of the change in the natural history of pneumonia and the effects of antibiotics a rather paradoxical position has arrived. To-day a far wider thoracotomy is often being performed on reasonably fit patients than in the pre-war days when a small rib resection was called for in patients who were often seriously ill.

The subacute or "missed" empyema.—Antibiotics have so altered the course of pneumonia that the classification of empyema into syn-pneumonic and meta-pneumonic types has become meaningless. Few patients with pneumonia are admitted to hospital as recovery at home is usually rapid. The flat temperature after the crisis of lobar pneumonia followed by the insidious rise of pyrexia which enabled the good ward sister to diagnose "empyema" is a piece of history. In streptococcal bronchopneumonia so often associated with a simultaneous purulent effusion the picture has altered even more. A patient may be sitting up at home reading a newspaper with a stony dull percussion note over the base. Indeed, the general well-being of a patient with a normal temperature may lead to the omission of even a perfunctory percussion of the chest. In such patients effusions may develop into a subacute or chronic empyema only detected because of the persistence of ill-health, lassitude and cough. The correct diagnosis may be made at an out-patient visit. The pus may be sterile and this provides diagnostic difficulties such as the suspicion of tuberculosis; much fibrin is often present.

17 patients in Table I are noted as having been treated by "decortication". These patients though showing varying degrees of illness were all well enough to be treated by a wide thoracotomy under general intratracheal anæsthesia. The wide incision enables removal of all the empyema contents and the rind of exudate covering the lung which is completely liberated. The anæsthetist then increases the intratracheal pressure so that the lung fills most of the pleural cavity. Two intercostal catheters, one apical and one basal, are inserted and connected to an underwater-sealed drainage system to which suction pressure is applied through a small Roberts' motor. As soon as the post-operative radiographs show that lung re-expansion is complete, the tubes are removed, usually in from two to five days. The post-operative story in hospital is measured in days rather than in weeks as is the case when simple tube drainage has been employed.

Empyema not due to a precedent or accompanying pneumonia.—Probably most pleural empyemata seen to-day follow surgical operations such as excision of portions of lung for tuberculosis (due to a fistula) or operations on the œsophagus. It is surprisingly rare after excisional surgery for bronchiectasis.

Empyema, however, may be secondary to underlying lung disease such as bronchiectasis and carcinoma of the lung. The train of events is that bronchial occlusion is followed by lung abscess, or pneumonia and then a slow leak of pus into the pleural cavity may produce a confusing picture. This does not necessarily make excisional surgery out of the question. It indicates the need for bronchoscopy in some patients. Actinomycosis and other unusual fungus and parasitic infections of the lung may be responsible.

Staphylococcal pneumonia, especially in infants, may be complicated by empyema formation. The large distended abscess cavities seen in this condition appear so alarming on the radiograph that a hasty opinion might favour drainage. It is, however, widely recognised that such patients require conservative management with adequate antibiotic treatment. If empyema development follows, the indications to resort to drainage should be resisted, reliance being placed on daily needle aspiration combined with local and parenteral antibiotic therapy.

Tuberculosis.—Empyema in this disease would require much time for discussion. It may develop spontaneously or more often is the complication of artificial pneumothorax or of resection operations. In its treatment a complicated set of procedures ranging from persistent aspiration to pleuro-pneumonectomy may be required. The principle of decortication is not infrequently applied and this may be combined with excisional operations such as lobectomy and a partial thoracoplasty. (Examples of this were shown on slides.) The modern aim is to avoid as far as possible the mutilating complete thoracoplasties that were in frequent use in the days of ill-applied pneumothorax therapy followed by total empyema.

Conclusions

True empyema is not common, nor often a fatal disease. Its natural history has been completely changed by modern antibiotic and chemotherapy and the old differentiation into syn- and meta-pneumonic types has become meaningless.

The three aims in treatment, the relief of respiratory embarrassment, the control of infection and the restoration of lung and chest-wall function, depend on a shrewd application of aspiration, chemotherapy and antibiotic therapy; this alone will suffice in infants but in most instances in adults surgical evacuation of the empyema contents is necessary: this can be safely carried out by a moderately wide thoracotomy with complete toilet of the cavity often involving decortication. The drainage after this operation is normally by two intercostal catheters which are removed as soon as there is radiological evidence of full lung re-expansion.

If simple drainage is employed, the tube must not be removed until the empyema pocket is known to be obliterated; this is shown by Lipiodol sinograms. Intercostal drainage is an obsolete practice. Throughout the whole course of treatment, breathing and chest wall exercises are important.

A brief allusion has been made to pleural empyema not due to classical pneumonia and a reminder given that to-day carcinoma of the bronchus is a not uncommon cause of empyema.

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The Preservation of Arterial Grafts by Freeze-drying

By C. G. ROB, M.C., F.R.C.S.

Professor of Surgery, St. Mary's Hospital, London

ARTERIAL grafts have been used for about six years in the treatment of abnormalities in patients and for nearly fifty years in experimental animals. Carrel was awarded the Nobel prize in Medicine in 1912 for his work on blood-vessel grafting and Lexer in 1913 reported that he had resected 3 aneurysms and restored continuity in each patient with an autogenous vein graft.

Of recent years the indications for blood-vessel grafting have increased:

(1) Congenital abnormalities, e.g. a long coarctation.
(2) Aneurysms and arteriovenous fistulas.
(3) Wounds (*a*) as a primary measure,
(*b*) if symptoms develop after ligation.
(4) Primary thrombosis, e.g. popliteal artery.
(5) After some emboli.
(6) Occasionally in malignant disease.
(7) In some patients with arteriosclerosis.

Senile obliterative arterial disease or arteriosclerosis is a general disease which affects the arteries of the whole body and the operation of artery grafting can only produce a local effect. In this disease, therefore, it is only justified in exceptional circumstances. To make this point clear, of those patients who have consulted us on account of intermittent claudication due to arteriosclerosis and who were anatomically suitable for grafting only 1 in 30, or 3%, has been grafted by us.

This increase in the use of blood-vessel grafts has focused attention upon the storage of arteries. It is this branch of blood-vessel grafting which I intend to discuss.

The first artery bank was started by Carrel in the first years of this century. He stored his grafts in Locke's solution at a degree or so above freezing point in a refrigerator. The results in experimental animals were good. In 1909 Levin and Larkin reported a series of experiments in which arteries were preserved in 4% formaldehyde; their results were not encouraging. But in 1919 Guthrie stated that a vena cava preserved for sixty days in this way had functioned satisfactorily for eleven years as a graft in the carotid artery of a dog. Many others have repeated this work; to-day it can be stated that formalin-preserved grafts are inferior to refrigerated, frozen or freeze-dried vessels.

The next advance came in 1949 when Gross, Bill and Peirce described their human artery bank. They modified Carrel's technique and stored their arteries in 10% homologous serum in a balanced salt solution to which was added a buffer, a pH indicator, streptomycin and penicillin. Arteries stored in this way have now been used in many hospitals and the results have been excellent provided that the period of storage has not exceeded six weeks. Unfortunately this time limit has proved to be a real obstacle because suitable donors are hard to obtain.

Frozen storage (Eastcott and Hufnagel, 1950) at temperatures of between −20° C. and −79° C. solved the problem of storage time. Arteries stored in this way have been kept for years and have proved to be satisfactory in clinical practice. The main defect of frozen storage has been that the grafts are difficult to transport from hospital to hospital and a costly deep-freeze is necessary.

FREEZE-DRYING

This technique was first used for preserving arteries by Marragoni and Cecchini (1951). They reported that of 20 such grafts the results were excellent in 16 of the animals. 9 freeze-dried arteries from our bank have been used in patients with satisfactory early results in 7. Figs. 1 and 2 show such a graft in position.

Theory of freeze-drying.—Every substance can be in a solid, liquid or gaseous state, depending upon the temperature and the pressure.

It is possible by altering the pressure to convert a solid such as ice to a vapour without the solid melting and becoming a liquid. This process is known as sublimation. In the case of a mixed solution such as human tissue fluids, the eutectic point is the temperature at which freezing begins. "Freeze-drying" or "drying by sublimation" makes use of the fact that removal of the water from mammalian and other cells by sublimation does not denature the proteins (denaturation is a tendency for protei

FIGS. 1

FIG.

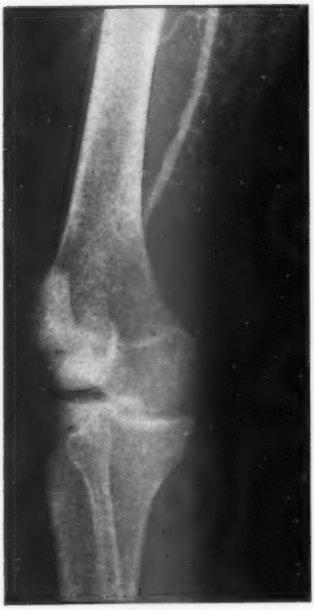

FIG. 1.

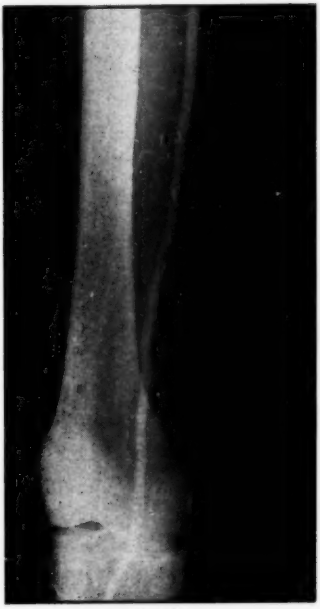

FIG. 2.

FIGS. 1 and 2.—Arteriograms taken before and after reconstruction of the popliteal artery with a freeze-dried arterial homograft.

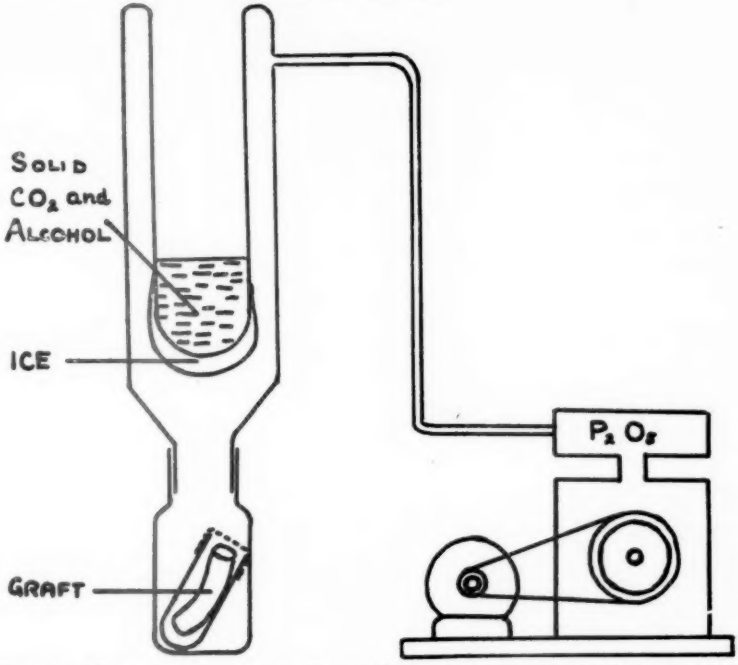

FIG. 3.—Diagram of the apparatus used in the Surgical Unit at St. Mary's Hospital for freeze-drying arteries.

molecules to aggregate and become insoluble as when an egg is boiled). This means that some human tissues after freeze-drying are indistinguishable macroscopically and microscopically from normal tissues; they are, however, dead.

Technique of freeze-drying arteries.—The vessels are removed with full aseptic precautions from a suitable donor. They are then placed in a sterile empty pyrex tube and frozen to −79° C.; they are kept frozen until dry.

We freeze-dry by subjecting the frozen graft to a high vacuum (0·05 mm.Hg approximately). Fig. 3 illustrates the method. With this low pressure water is freely able to leave the graft as vapour which is collected as ice on the condenser; any water vapour which passes this is trapped in the P_2O_5 just before it reaches the vacuum pump. The graft must remain frozen until most of the water has been removed. This is achieved in the case of small volumes of material by the loss of the latent heat of evaporation and, to date, we have relied on this to keep the grafts frozen during drying. The experimental work which shows that external cooling is unnecessary during the drying of an artery will be published elsewhere by H. H. G. Eastcott. Others, notably those at the Naval Medical Center at Bethesda, Maryland, have used external cooling. This phase of drying by sublimation lasts between five and nine hours depending upon the bulk of material to be dried; by this time 95% or more of the water has been removed and the grafts have warmed to room temperature since the cooling effect of evaporation has now ceased.

After this process of primary drying has continued for a full working day the vacuum is broken and the grafts transferred to a desiccator which contains a tray of P_2O_5. This desiccator is then evacuated and the grafts left for at least three or four days at room temperatures, during which period of secondary drying a further 3% or 4% of the original water content is removed by the P_2O_5, leaving only 1% to 2% still present in the artery. The final stage consists of the removal of the tubes from the desiccator, their closure with a special rubber bung, final evacuation via a hypodermic needle passed through the rubber and sealing with picien wax. It is stressed that the most careful aseptic technique must be practised throughout because freeze-drying in this way only reduces the number of bacteria; it does not sterilize the grafts.

To reconstitute the artery sterile isotonic saline should be introduced without breaking the vacuum until the tube is full. The graft requires about thirty minutes to rehydrate, after which period the branches are tied and it is made ready for use.

Grafts preserved by freeze-drying can be stored for many years at room temperatures and carried in the surgeon's instrument bag. In my opinion no surgeon should operate on such a condition as coarctation of the aorta without a suitable graft being available for him to fall back on if an end-to-end anastomosis proves to be impossible.

The follow-up on the freeze-dried grafts is too short but the early results show 7 immediate successes and 2 failures. I would also like to stress the much poorer results when the reason for grafting has been an arteriosclerotic thrombosis.

The Best Way to Store Arteries

In the present state of our knowledge freeze-drying is the most convenient way of storing arteries. It has one possible theoretical disadvantage: the graft is dead; and one practical disadvantage: the donor must be even younger than with frozen storage—less than 25 years of age. Frozen storage in either an empty tube or in 15% glycerol saline has given very good results, and we have only been using freeze-dried arteries for one year. To summarize, we know frozen arteries work well and we think that freeze-drying will be as effective but as yet we are not sure.

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Mr. D. N. Ross pointed out that although formalin preservation of arteries had been given up because of the high incidence of failure and calcification there still remained the task of sterilizing arterial segments removed under non-aseptic conditions. With this in mind he had used a buffered formalin solution as a means of sterilizing contaminated graft segments and these were then frozen or freeze-dried for subsequent storage. The minimum period of immersion in formalin to ensure sterility had been found to be eighteen hours, after which the sterilized segment was washed in saline to remove excess formalin. Implantation of arterial segments treated in this fashion had given encouraging results. Further details of the technique have been published in *Guy's Hospital Reports* (1954) **103**, 71.

Section of Otology

President—R. R. Simpson, F.R.C.S.Ed.

[*December* 4, 1953]

DISCUSSION: THE RAMSAY HUNT SYNDROME

Introduction

Mr. Kenneth Harrison, Department of Otolaryngology, Manchester University:

During recent years I have observed and treated a series of 12 cases of the Ramsay Hunt syndrome in Professor Victor Lambert's Department at the Manchester Royal Infirmary.

It was in Boston in June 1906 that Dr. Ramsay Hunt presented his classical communication to the American Neurological Association entitled "Herpetic Inflammation of the Geniculate Ganglion. A New Syndrome and Its Complications". He believed the syndrome to be dependent on a specific herpes zoster inflammation of the geniculate ganglion. This ganglion is situated on the facial nerve in the depths of the internal auditory meatus at the entrance to the bony fallopian canal (Fig. 1).

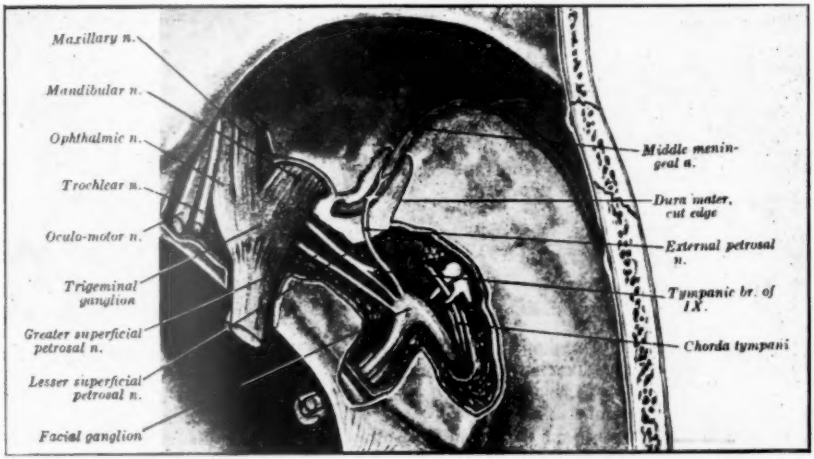

FIG. 1.—The geniculate ganglion of the facial nerve and its branches (reproduced from Gray's Anatomy by permission of Messrs. Longmans Green).

Classification.—He classified the different clinical types of the syndrome as follows:

(1) Herpes oticus, with no neurological signs.
(2) Herpes oticus with facial palsy.
(3) Herpes oticus with facial palsy and auditory symptoms.
(4) Herpes oticus with facial palsy with accompanying auditory and labyrinthine symptoms.

Each type is characterized by "pre-herpetic pains" localized to the ear and mastoid region. This is followed by a zoster eruption of variable extent, occurring in the area called by Ramsay Hunt the "zoster zone" for the geniculate ganglion (Fig. 2). It includes the tympanic membrane, external auditory canal and meatus, and the following areas on the lateral surface of the auricle, the concha, antitragus and the anti-helix and its fossa. Sometimes the eruption is seen on the postero-mesial surface of the auricle and the adjacent skin over the mastoid process.

The facial paralysis may occur soon after the appearance of the eruption, it is of the peripheral type and usually complete. Hunt considered that the motor fibres of the nerve were involved in the zoster inflammatory process.

Sometimes accompanying the foregoing symptoms there is loss of hearing and may be an associated tinnitus. He ascribed the auditory symptoms to an extension of the inflammation to the auditory nerve which is in close relationship to the geniculate ganglion.

He considered his fourth type to be a severe manifestation and along with the symptoms already mentioned were added those of vertigo.

He thought that the zoster inflammation extended along the nerve sheaths to the auditory nerve endings or *possibly* that the "ganglia" of the auditory nerve may be primarily involved in the zoster infection.

Hunt also emphasized a group of cases with zoster eruption and auditory symptoms *without* facial palsy. He believed this group may be due to a primary involvement of the "ganglia" of the auditory nerve, because he thought it improbable that an inflammation could extend to the auditory nerve without involving the motor fibres of the facial nerve.

He considered that the cutaneous sensory supply of the geniculate ganglion is an irregularly cone-shaped area, the apex corresponding to the tympanic membrane and the base situated on the external surface of the auricle; this is his so-called "zoster zone".

There may be "post-herpetic pain" which may persist for a considerable time after the zosteric eruption has disappeared.

It was in 1915 in his later investigation on the syndrome that he observed and described a zoster eruption sometimes occurring within the buccal cavity on the soft palate and the anterior two-thirds of the tongue (Fig. 3).

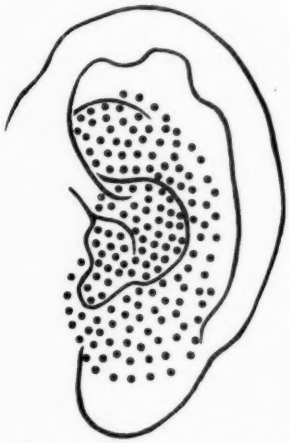

FIG. 2.—Distribution of vesicular rash over the "zoster zone" on the auricle (reproduced from *Brain*, **38**, 427, by permission of the Editor and of the publishers, Messrs. Macmillan & Co.).

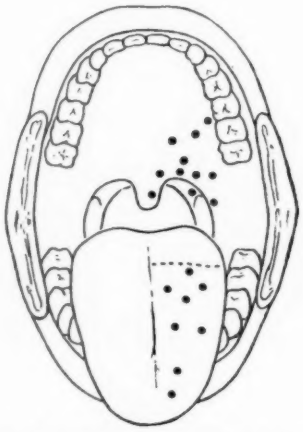

FIG. 3.—Distribution of vesicular rash over the soft palate and anterior two-thirds of the tongue (reproduced from *Brain*, **38**, 429, by permission of the Editor and of the publishers, Messrs. Macmillan & Co.).

Following this introduction of Ramsay Hunt's conception of the syndrome bearing his name, the clinical picture of the cases under review will be described.

Cases Under Review

Since August 1949 12 cases of the syndrome have been observed and studied. It is thought best to assign the cases to the classification used by Ramsay Hunt. 8 of them were similar to his clinical group four, being herpes oticus with facial palsy and accompanying deafness and vertigo. 2 of the series were in his group three, herpes oticus with facial palsy and deafness. One of the remaining cases was a simple otic zoster with facial palsy, and the other a herpes facialis involving the mandibular division of the trigeminal nerve with an associated herpes oticus and facial palsy.

Occurrence.—All the cases have been seen between August 1949 and August 1953.

In August 1949 there were 4 cases, in May 1952, 2 cases, and in August 1953, 2 further cases; the other ones occurred singly and quite sporadically.

They all occurred between February and September of each year.

Age and sex incidence.—The patients were all adults between the ages of 33 and 76 years and included 10 females and 2 males.

Clinical Features

The cases were all unilateral.

Usually there were prodromal symptoms of headache and lassitude with accompanying slight fever, the temperature being in the region of 99·5° to 100° F. These symptoms continue for a day or two.

Local symptoms then usually occur and it is during this stage that the patients are first seen. First *pain* is complained of and it is of varying distribution and character. Earache is most frequently present and it is either felt superficially around the auricle or deeply within the meatus. Sometimes there may be generalized pain in the head but more frequently it is localized in the face and lower jaw and may radiate down the neck. It is often characterized by a burning or pricking sensation and there is an accompanying hyperæsthesia. At times the pain is actually neuralgic, and is referred to as pre-herpetic neuralgia.

Zosteric eruption.—Within a few days a zosteric eruption occurs. It is usually seen on the auricle and the external meatus, sometimes on the soft palate and occasionally on the anterior two-thirds of the tongue.

Eruption on the auricle and external meatus.—The skin of the conchal area of the auricle becomes reddened, swollen and tender and within a day or so vesicles are visible (Fig. 4).

FIG. 4.—The vesicular rash confined to the conchal area of the auricle.

In our experience the vesicular rash has been confined mostly to the concha, anti-helix and its fossa and the external meatus. Vesicles on the drumhead have not been a common feature and no eruption has been seen on the postero-mesial surface of the auricle and the adjacent skin of the mastoid process. After the vesicles heal they may leave small scars.

In only one of the cases was there any facial eruption and this was widely distributed over the region supplied by the mandibular division of the trigeminal nerve. When the zoster eruption develops the pre-herpetic pain usually abates, but there is usually localized pain due to the eruption and accompanying adenitis.

Sometimes the walls of the external meatus may be so swollen that a clear view of the deeper parts of the canal is impossible.

Frequently the pre- and post-auricular lymph nodes are enlarged and tender and occasionally the upper deep cervical group.

In 2 cases perforation of the tympanic membrane was observed with accompanying inflammation of the meatal walls. At first it was puzzling as to whether the perforations were of recent origin due to the zoster infection or long-standing ones. In each case the patients denied previous aural disease, but after questioning and due consideration it was decided they were long-standing defects. In neither case did the perforation show any sign of healing.

Eruption of the soft palate and tongue.—In 5 of the patients small discrete vesicles were seen on the soft palate of the affected side and in 3 of these there were vesicles on the anterior two-thirds of the tongue with accompanying soreness. No noticeable pre-herpetic pain has been complained of within the buccal cavity, thus the vesicles will be missed unless particularly searched for.

Facial palsy (Figs. 5 and 6).—A lower motor neurone palsy was present in each case and usually of quite severe degree. There was always a latent period before the onset of the palsy and it was anything between one and ten days following the appearance of the vesicular rash. This latency may

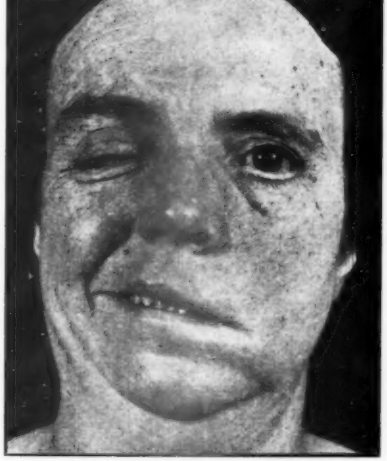

FIG. 5.—Complete facial palsy.

FIG. 6.—Wide distribution of vesicular rash on the auricle.

depend on the time it takes the inflammation to extend from the geniculate ganglion to the motor fibres.

Before the appearance of the palsy it may be quite difficult to make a correct diagnosis.

Paresis of the soft palate.—In none of the cases was a paresis of the soft palate noted. This finding was observed by Ramsay Hunt, and it has been reported occasionally in the literature.

Loss of taste.—In half the cases there was loss of taste over the anterior two-thirds of the tongue on the affected side. The taste sense always returned, usually within a period of a few weeks.

Deafness.—In 10 there was an accompanying perceptive deafness in the affected ear. Audiometric tests showed an increasing loss in the higher tones particularly at a frequency of 2048 and above (Fig. 7).

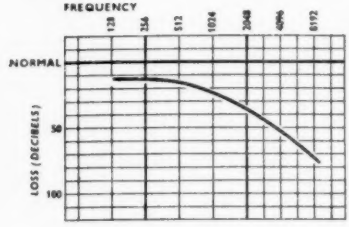

FIG. 7.—Pure-tone audiometric curve showing hearing loss in the higher tones particularly at a frequency of 2048 and above.

In 3 the deafness was bilateral and this was quite a surprising finding, the significance of it will be discussed later.

Tinnitus.—Was not a constant symptom even in the deafness cases and occurred in 4 of them. It was not unduly troublesome and always disappeared within a short time.

Vertigo.—Was present in 8 patients of the series and usually occurred within the first week of the infection. It was mostly severe with accompanying vomiting, and usually lasted from a few days to a number of weeks and necessitated rest in bed.

Even after the acute vertigo settled there was a feeling of unsteadiness, which in some cases lasted for many months, and in certain of the most severe ones the unsteadiness persisted for two to two and a half years.

In the early stages of the vertigo a spontaneous fine horizontal nystagmus was seen towards the sound side. Hot and cold caloric tests were carried out as soon as the patients were sufficiently fit and in two-thirds of the group with vertigo an absent response was noted on the affected side. The tests have been repeated at intervals since, sometimes as long as four years after the initial infection and no recovery has been noted.

The 3 patients with bilateral perceptive deafness had an accompanying vertigo and unilateral herpes and facial palsy. The results of the caloric test were interesting; there was an absent response on the side with the facial paralysis but quite a normal reaction on the other side.

Post-herpetic pain.—Post-herpetic pain has not been a troublesome symptom in any of the cases.

INVESTIGATIONS

(1) White cell count—no significant change noted.
(2) Audiometric and caloric tests—the results of these have already been described.
(3) Lumbar puncture.

In 5 of the cases lumbar puncture was performed. In 3 of them there was an increased mononuclear cell count ranging from 6–159 cells and a raised protein of 45–65 mg./100 ml. Within a few weeks the fluid was normal.

Greenfield and Carmichael (1925) state that a mononuclear pleocytosis may occur in herpes zoster. They do not consider there is any relationship between the severity of the disease and the degree of change in the cerebrospinal fluid. Lange (1908) described the facial and auditory nerves as having a common sheath formed by the continuations of the meninges. The auditory nerve at its entrance into the internal meatus is surrounded by a loosely adherent process of arachnoid until it reaches the fundus of the canal, at which point the membrane becomes adherent to the bony wall. This arachnoid covering follows the facial nerve for a short distance in the fallopian canal where it also becomes attached to the bony wall.

It is thought that because of these attachments of the arachnoid, the ganglia of the facial and auditory nerves are *intrameningeal*, and thus when involved in zoster infection changes may result in the cerebrospinal spinal fluid.

TREATMENT

There is no specific treatment for herpes zoster infection.

It is important to relieve the "pre-herpetic pain" and prevent infection of vesicular eruption.

The facial paralyses were treated by galvanism and, if possible, it is preferable to treat daily. It is

thought that galvanic stimulation aids in preventing further muscle wasting and delays fibrosis. It helps in maintaining the blood supply and when the nerve begins to conduct there is usually a better recovery.

Some surgeons practise decompression of the facial nerve in these cases and I am most interested to know if this does aid recovery.

In a number of cases, actually 6, a trial was made with the newer antibiotic drugs. Chloramphenicol was used in 3 and Aureomycin in the other 3. In only 1 case was there dramatic improvement.

It occurred in a female patient aged 33 who had the severe manifestation of the syndrome accompanied by symptoms of deafness and vertigo. Chloramphenicol was prescribed. Within a few weeks the perceptive deafness improved to within normal limits, the facial paralysis recovered and the vertigo disappeared. The caloric reaction has remained absent, even after a period of eighteen months.

The other cases showed no rapid improvement and progress was slow.

Prognosis

Post-herpetic pain has not been a troublesome symptom.

Recovery of facial palsy.—Only 10 of the cases can be traced. In half of them recovery was complete. In the other half 3 showed partial recovery *only* after a period of two years or more. It is too early as yet to know just how much recovery will take place in the other 2, as it is only three to four months since the palsy occurred.

Taste.—Always recovered and usually within a few weeks.

Deafness.—Only in half the cases of perceptive deafness was there improvement to within normal limits. In the 3 patients who presented with bilateral deafness, the pure-tone air conduction curves have remained about the same, 2 four years after the infection and the other three years.

Vertigo.—The vertigo has always disappeared sometimes taking many weeks, occasionally months. Even then certain patients have complained of unsteadiness which has lingered for as long as two to two and a half years.

Comment

The Ramsay Hunt syndrome appears to be quite rare, as only in 12 cases was the diagnosis made during a four-year period.

One-third of them occurred during the month of August 1949.

Two-thirds of the cases are placed in Ramsay Hunt's fourth group, in which there is accompanying deafness and vertigo, and he considered this group to be the severest manifestation of the infection.

It is thought that the zoster inflammation may extend from the geniculate ganglion of the facial to C.N. VIII via the communicating branches between the two nerves in the internal auditory meatus and at this level they are within a common sheath, or quite possibly there may be a primary involvement of the "ganglia" of C.N. VIII.

The 3 cases which were found on audiometric testing to have bilateral perceptive deafness were puzzling. There were no records of the patients' hearing before the infection, and they all denied any deafness. On the contralateral side in which there was deafness only, the spiral ganglion may have been *primarily* involved or there could have been a more central involvement. I have not found similar cases described in the literature, but Stewart (1927) reported a case in which there was a marked unilateral Ramsay Hunt syndrome involving C.N. VII and VIII and on the opposite side the vestibular ganglion *only* was thought to be involved, as evidenced by absent response to the cold caloric test.

In one of the cases there were additional small vesicles on the posterior pharyngeal wall and on the lateral border of the epiglottis and aryepiglottic fold; the movements of the vocal cords were quite normal. This type of case indicates involvement of C.N. VII, VIII, IX, and X. McKenzie (1915) reported a case of unilateral herpes zoster in which C.N. VII, VIII, IX, and X were involved. In his case the recurrent laryngeal nerve was implicated, too, resulting in a vocal cord palsy which recovered quite spontaneously. In 1943 Negus and Crabtree described a somewhat similar case in which there was involvement of C.N. VII, IX, and X. Along with marked vesicular eruptions, there were unilateral paralyses of the face, soft palate, constrictors and vocal cord; satisfactory recovery took place.

In none of these cases was the complement-fixation test performed to identify the zoster virus, as the facilities were not available. In 1933 Brain and Aitken carried out serological tests on cases of facial palsy and reached the following conclusions: A series of 9 cases of Bell's palsy *with* zoster-like eruptions of the auricle and meatus was found to contain antibodies to zoster virus as shown by a positive complement-fixation test. A series of 22 cases of Bell's palsy *without* zoster-like eruptions was found to have positive complement-fixation tests *in 4 cases* only. In these 4 cases it was thought that there may have been eruptions in the external auditory meatus which had been missed; thus it is always important to examine the meatus in the case of Bell's palsy.

Another point arising is that an eruption may be very slight or even missing, the so-called *herpes sine herpete.* If this is so, such cases would be classified as ordinary Bell's palsy unless there were signs of obvious involvement of C.N. VIII.

In none of the cases has any eruption been seen within the nasal cavity. This finding was reported in 2 cases of the Ramsay Hunt syndrome by Wakeley and Mulvaney in 1939; there was "slight serosanguineous nasal discharge" and small discrete vesicles were seen within the anterior part of the nostril on the affected side and also a vesicular rash on the hard and soft palate.

Conclusions

(1) The Ramsay Hunt syndrome appears to be an uncommon clinical entity, only 12 cases presenting during the four-year period from August 1949 to August 1953. One-third of the cases occurred during one particular month, August 1949.

(2) The sex incidence was predominantly female occurring in 10 of the series.

(3) The clinical picture of the syndrome is puzzling, making early diagnosis difficult. Antecedent otalgia may be misunderstood before the vesicular eruption appears. Even at this stage diagnosis can be problematical, and the buccal cavity should always be examined for the presence of vesicles on the palate and anterior two-thirds of the tongue.

(4) In this series a zoster infection involving the facial and auditory nerves was common, occurring in 10 out of the 12 cases. Involvement of C.N. IX and X appears to be very rare, occurring once only and there appear to be few reported cases in the literature.

(5) Complement-fixation test for zoster virus:

A positive test may be very helpful as confirmatory evidence of a zoster infection and particularly in cases of peripheral facial paralysis when no vesicular eruption can be seen.

(6) The complete recovery of the facial paralysis only occurred in half the cases traced.

(7) The perceptive deafness may be permanent as in 5 cases of the series, and sometimes is quite severe, but vertigo is never persistently troublesome.

(8) At present there does not appear to be any specific treatment for zoster infection.

I wish to thank my Chief, Professor Lambert, for allowing me to carry out this investigation and for his guidance and helpful criticism. My thanks are also due to Dr. R. G. W. Ollerenshaw and the staff of the Department of Medical Illustration at the Manchester Royal Infirmary.

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Dr. John D. Spillane:

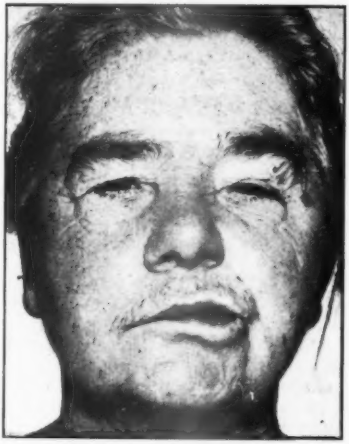
James Ramsay Hunt (1874–1937) was an American neurologist of Quaker Philadelphian heritage. He made definite contributions to neurological science. He described a form of akinetic epilepsy, certain cerebellar phenomena and occupational palsy of the deep palmar branch of the ulnar nerve. At one time or another three or four of his syndromes have been christened Hunt's disease. But his main interest throughout his life concerned the syndrome of "geniculate zoster". Indeed, his first paper on this subject was published in 1907 and the last was in the year of his death in 1937.

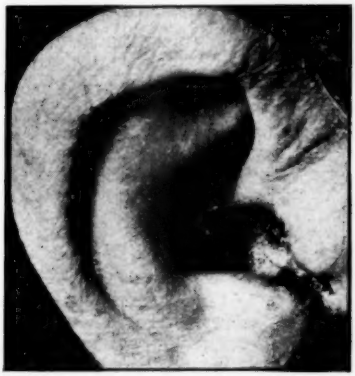
Ramsay Hunt looked on herpes zoster of the head and neck as due to involvement of ganglia containing the posterior spinal or unipolar type of cell. He observed, as others had done before him, that herpes oticus was sometimes combined with ipsilateral facial palsy. Some patients affected in this way suffered from tinnitus, deafness and vertigo. Hunt postulated that the geniculate ganglion, the homologue of the posterior spinal root ganglia, situated on the exclusively motor facial nerve, was in fact the site of infection in this type of case. He obtained no pathological proof of this theory but for over thirty years he defended and elaborated it with great, but in my view needless, ingenuity. He considered that swelling of the geniculate ganglion caused pressure on the facial nerve with resulting palsy. The auricular eruption was thought to indicate that there were in fact in this apparently motor facial nerve sensory fibres with cutaneous endings in a small area in the centre of the auricle which Hunt called the geniculate zone. When trigeminal or cervical herpes developed in association with facial palsy Hunt concluded that the gasserian or cervical ganglia as well as the geniculate ganglion were also affected. It was this conception of simultaneous ganglionitis which Hunt elaborated. But here he encountered difficulties. With trigeminal or cervical ganglion infection why should an associated facial palsy be attributed to involvement of the geniculate ganglion in the absence of herpes oticus? Was he to assume that this ganglion is infected and swollen so as to cause pressure on the motor fibres of the facial nerve and yet not manifest itself in the ordinary way by herpes in its alleged sensory zone?

Hunt was able to procure a post-mortem on one of his cases, a man of 48, who died eighty days after an herpetic infection causing facial palsy and characteristic eruption of occipito-cervical distribution. There was no auricular herpes. Unfortunately, the geniculate ganglion was never examined but degeneration was found in the third cervical ganglion and its posterior root and in the nerve of Wrisberg between the geniculate ganglion and the pons. The post-mortem described in 1944 by

Denny-Brown and his colleagues was of a similar case who died sixty-four days after the onset of the illness. There were facial palsy and herpes of the second cervical distribution. It cannot be said with certainty that in this case there was an herpetic eruption in Hunt's "geniculate zone". The skin in the external auditory canal was "swollen, red and desquamating". The vesicular eruption was "in the right occipital and posterior auricular regions". Namely, in the second cervical dermatome. The photographs reveal only the facial palsy and the occipital herpes. At autopsy the geniculate ganglion was normal but the facial nerve was infiltrated throughout its course—above and distal to the geniculate ganglion. The second cervical ganglion was destroyed by the virus. The third cervical ganglion was practically intact. The ninth and tenth ganglia were not examined. This case demonstrates that in herpes of the head and neck damage to the facial nerve may occur without geniculate ganglionitis. It does not prove that geniculate ganglionitis does not occur and could not cause facial palsy and herpes oticus. Indeed, in view of the demonstration that herpetic infection of the relatively remote cervical ganglia can cause a neuritis of the facial nerve there can be no objection to the idea of geniculate infection doing likewise. But we now know that invasion and not compression of the facial nerve is the likely mechanism of involvement.

Confusion arises when the term Ramsay Hunt syndrome is applied to facial palsy with trigeminal or occipito-cervical herpes. There is no doubt that in such cases the anterior and posterior surfaces of the external ear respectively may be affected. The term should be restricted to those cases in which the herpes is confined to the concha and meatus (Figs. 1 and 2). If there is also herpes of glosso-





FIGS. 1 and 2.—Ramsay Hunt syndrome illustrating peripheral facial palsy with herpes zoster of cervical II and III distribution and with herpetic eruption in the conchal zone of the ear. There was no herpetic involvement in the mouth, pharynx or larynx. The facial paralysis developed twelve days after the first appearance of the herpetic rash on the neck. Facial paralysis may be a complication of herpes zoster in any zone of the head and neck, but is most commonly encountered in association with cervico-occipital zoster.

palato-pharyngo-laryngeal distribution then the IX and X ganglia are clearly implicated and otitic herpes could then be interpreted as occurring in the distribution of the auricular branch of the vagus nerve.

Sensory fibres to the concha from the facial nerve.—That meticulous observer Gowers wrote that in facial palsy: "I have several times found an area of anæsthesia on the front and back of the concha in the region of skin supplied by a nerve given off by the facial as it emerges." Gowers (1888) thought it may have derived from the V nerve. Larsell and Fenton (1928) demonstrated in man fibres from the pars intermedia of the facial nerve joining the auricular branch of the vagus nerve and being distributed to the skin of the auricle. Furlow (1942) stimulated the exposed pars intermedia of the facial nerve at open operation in a conscious patient and produced sharp meatal pain. Section of the nerve was not followed by any area of sensory loss but the meatal neuralgia ceased. Similar relief of meatal pain has been obtained in glossopharyngeal neuralgia after section of the glossopharyngeal nerve.

Can the method of topographic analysis of the facial palsy in the Ramsay Hunt syndrome determine whether the lesion is supragenicular, geniculate, or infrageniculate? It is most unlikely to do so for several reasons. Firstly, the lesion in the facial nerve may be distributed throughout the course of the nerve in a patchy and uneven manner as in Denny-Brown's case. Secondly, the facial paralysis may be incomplete so that the absence of such signs as are used to determine the level of a lesion in the facial

nerve are then unreliable guides. Thirdly, the spread of infection or degeneration along axones may secondarily implicate certain functions such as tear secretion or taste sensation.

But if we assume the responsible lesion in the Ramsay Hunt syndrome is in the geniculate ganglion and completely involves the facial nerve, can this be in any way deduced clinically? Paralysis of the stapedius muscle and the lacrimal portion of the orbicularis oculi muscle and loss of sensation on the anterior two-thirds of the tongue would ensue, but hyperacusis (phonophobia), epiphora and taste loss could also obviously arise in an infrageniculate lesion (Fig. 3).

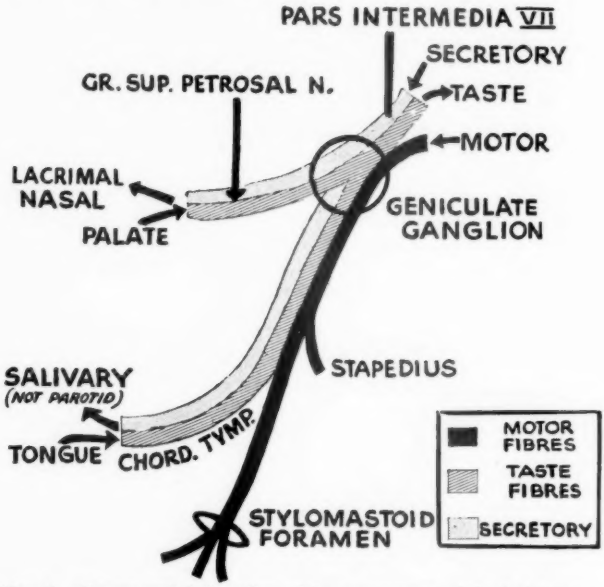


FIG. 3.—Course and designation of the components of the facial nerve.

The sensory root of the facial nerve, the pars intermedia, contains fibres transmitting the sensation of taste from the anterior two-thirds of the tongue and probably also from the palate. The former reach the geniculate ganglion via the chorda tympani nerve. Harris (1952) has effectively reasoned that taste fibres from the palate travel via the great superficial petrosal nerve to the geniculate ganglion. He thinks that there can now be little if any doubt that the gustatory fibres of the chorda tympani and the great superficial petrosal nerve pass centrally to the geniculate ganglion and thence by the pars intermedia to the medulla and pons. There has always been considerable divergence of view with regard to the supragenicular pathway of taste fibres and even the direction of transmission of impulses in the great superficial petrosal nerve. Harris (1952) suggests that the presence or absence of loss of taste on the palate may be regarded as a clue to the position of the lesion in peripheral facial palsy. Supragenicular or geniculate lesions should lead to loss of taste on the palate as well as on the tongue itself. However, I do not know of any observations on this point in the Ramsay Hunt syndrome. I have not found taste retained on the anterior two-thirds of the tongue on the side of the lesion in any case I have examined. Whether palatal gustatory sensibility proves a sufficiently reliable test I very much doubt.

Other sensory fibres in the facial nerve.—Secretory fibres to the salivary, lacrimal and nasal glands are present in the sensory root of the facial nerve above the geniculate ganglion. Those to the lacrimal and nasal glands leave the geniculate ganglion and travel in the great superficial petrosal nerve. Fibres destined for the submandibular and sublingual glands travel via the facial nerve and the chorda tympani. The parotid gland receives its secretory fibres from the auriculo-temporal branch of the mandibular nerve. Dryness of eye and nose, but not of the mouth, on the side of the lesion, may therefore indicate a geniculate *or* supragenicular lesion.

Tschiassny (1946) used the involvement or otherwise of taste sensation and tear secretion to analyse the site of the facial nerve lesion in the Ramsay Hunt syndrome. His conclusions were that when facial palsy is associated with herpes of trigeminal or cervical distribution the lesion is below the geniculate ganglion. When the facial palsy is combined with auricular herpes as described by Ramsay Hunt, Tschiassny concluded that the lesion was at geniculate ganglion level. However, this analysis was

based on the supposition, which is probably incorrect, that taste sensation is not lost in a lesion of the nerve of Wrisberg—that is in a supragenicular lesion. There is therefore no certain method of topographical analysis of facial palsy which will identify a lesion in the geniculate ganglion.

Pathology of herpes zoster.—The virus appears to spread from the meninges to the ganglia, thereby first affecting the peripheral ganglion cells. This explains why the eruption often begins in the median zone (Heilborn, 1950). It is abundantly clear that although the chief lesion is in the posterior root ganglion and is in the nature of a vascular disturbance (spinal ganglion apoplexy) lesions are found also in the posterior and anterior horn cells of the spinal cord, in the anterior and posterior nerve roots and the adjacent leptomeninges. There may even be encephalitis or myelitis. That is to say that the actual invasion of nervous tissues is more widespread than the eruption itself indicates. When there is motor paralysis associated with zoster in 90% of cases the paralysis and zoster are of the same segmental distribution (Taterka and O'Sullivan, 1943). The zoster usually precedes the paralysis by an interval of a few days or a few weeks. In the upper limb it is usually the deltoid and in the lower limb the quadriceps muscles which are affected. There thus seem to be factors of susceptibility and extension of infection by nervous pathways. In the case of zoster of the head and neck the facial nerve is the most vulnerable. Paralysis of the III, IV, V or VI cranial nerves is a rare occurrence. In trigeminal herpes facial nerve paralysis is commoner than trigeminal paralysis. The various clinical patterns are probably determined by factors of susceptibility and modes of spread of infection in an intricate neural network.

Selectivity of the zoster virus.—Lastly, there is the factor of selective choice of the zoster virus for certain cells within an individual ganglion. In Head's (1910) original account of 416 cases of herpes zoster there were 22 of trigeminal distribution: mandibular division 2, maxillary division 2, ophthalmic division 18. If the gasserian ganglion can be invaded in this fractional manner by the herpes virus we might expect it to take place in other ganglia—including the geniculate, the IX and X—with a consequent restriction of the eruption.

Summary

(1) The facial nerve is the most vulnerable of the cranial nerves in zoster of the head and neck. Zoster infection is not confined to nerve ganglia. There is clinical and pathological evidence that it may cause neuritis of motor nerves. It is accordingly not necessary to postulate invasion of the geniculate ganglion when facial palsy is associated with herpes of the head or neck.

(2) Nevertheless there is no reason why zoster of the geniculate ganglion should not occur. Facial palsy would be a likely complication and the herpes, so far as is known, should appear in the conchal zone. No one has yet disproved Hunt's thesis that geniculate zoster is responsible for facial palsy with otitic herpes. The evidence indicates, however, that Hunt over-elaborated his thesis.

(3) The innervation of the external ear is complex, perhaps overlapping and variable. Aside from anterior and posterior auricular eruptions resulting from trigeminal and cervical ganglionitis, eruptions in the concha and meatus may result from VII, IX, and X ganglionitis.

(4) The geniculate level of a facial palsy cannot be identified clinically.

(5) The term "Ramsay Hunt syndrome" should be used only for those cases of facial palsy in which the herpes is restricted to the conchal zone. Only an autopsy in such a case can provide the solution to this problem of geniculate ganglionitis.

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Mr. J. P. Monkhouse: I should like to give a brief account of 3 cases which were admitted in October and November 1953 and January 1954, in order to point out the anomalies that occur in the Ramsay Hunt syndrome.

The first, a male aged 58, was admitted having had pain in the right ear for a week. He had a slight facial weakness, commencing herpes of the geniculate area but no vertigo or subjective deafness. An audiogram taken four days later showed a high tone loss on both sides, with masked bone conduction on the right following the same pattern, one which, at his age, might well have been present before his illness.

Five days after admission, the facial palsy was complete and the herpes very marked. On the sixth and thirteenth days, the facial muscles reacted normally to faradism and on the next day, the fourteenth, slight voluntary movement returned. In a month the face was fully recovered and there was a great improvement in hearing for high notes, both by air conduction and bone conduction, on the right. Three months later, his caloric reactions, which had not been tested before, were normal. He was treated with Chloromycetin for two days, followed by Aureomycin for five. No claim can be made on behalf of these drugs, particularly in view of the known variations in the course of this disease.

I want to emphasize the marked herpes, suggesting at the least a reasonably severe affection of the geniculate ganglion, coupled with a VII nerve that never shows the reaction of degeneration and recovers very quickly, a hearing loss that recovers and no evidence that the vestibular labyrinth was ever involved.

The next case was a male, aged 44. It is true that he never had any herpes, but on the other hand, he does not fit in with the usual conception of a Bell's palsy. Like the others, he had pain around the left ear for some days. Then there appeared a facial weakness and severe nausea, with constant vomiting and retching, which was accentuated by movement of the head. Two days later, the paralysis was complete and caloric tests showed a moderate left canal paresis. At ten days, the face began to move and, at the same time, an audiogram showed a left high tone loss by air conduction and bone conduction, with partial recruitment. At two months, the face and hearing had returned to normal. The left canal paresis was still present, and, to the same degree, at four months and, when tested again just recently, at twelve months.

In view of the severe vertigo, I thought I would try the effect of blocking the stellate ganglion, and it is interesting that except for one vomit while taking some tablets shortly after the injection, this symptom ceased abruptly. I had also heard at that time of an intravenous procaine drip as a treatment for facial palsy and this was given over the fifth and sixth days. Again it is impossible to assess the value of these procedures.

Here I want to stress, no herpes, complete facial palsy and objective involvement of both portions of the labyrinth. There was never R.D., the face began to recover in ten days and was well in two months. The hearing returned to normal, but the canal paresis persists.

The last case was a female, aged 32. Again there was pain, together with tinnitus in the right ear and a slight vertigo for four days before the onset of facial palsy. Two days later the palsy was complete, there was severe vertigo and vomiting, marked herpes of the geniculate region, loss of taste, no subjective deafness but she complained of hyperacusis. The mouth and palate were normal.

Denny-Brown *et al.* (1944) showed in one particular case in which a facial palsy was present that the geniculate ganglion was not affected and could not have been the cause of the palsy. They found a poliomyelitis and a neuritis of the facial nerve and put these forward as an alternative explanation of the Ramsay Hunt syndrome.

During a review of recorded cases, they would appear to admit the possibility of variation in the pathology when they say, "Nor is it certain that herpes zoster does not on occasion affect the geniculate ganglion", but they finish the article with the uncompromising statement, "Analysis reveals that the evidence for geniculate ganglionitis in the Ramsay Hunt syndrome is invalid".

My patient now came forward with a most interesting observation. She had caught a cold but said that it was only on one side. On the left side, her nose was hot, stuffy and running, while on the right, the side of her facial palsy, she just had not got a cold. It was evident that the secretory fibres of the parasympathetic were out of action and it seemed likely that the vasodilator fibres would be similarly affected, with the result that the nasal temperature should differ between the two sides. Dr. J. C. Seymour and Mr. J. W. Tappin, of the Ferens Institute of the Middlesex Hospital Medical School, made recordings, and I should like to thank them for a very great deal of help. Using a small thermocouple, connected to a large amount of electrical apparatus presided over by Mr. Tappin, it was possible to take instantaneous temperature readings.

Fig. 1 gives the dates on which the clinical signs and symptoms were first noted, together with their subsequent course, and the figures obtained during the investigation of the nasal temperatures. The sense of taste on the anterior two-thirds of the tongue was lost from the beginning and has not recovered. The secretion of tears was markedly diminished for two and a half months, when recovery commenced, and this was followed by a period of hypersecretion, suggesting that the recovering nerve was over-acting. The same phenomenon was observed in regard to nasal secretion.

Lacrimal secretion was tested by Schirmer's method and it must be emphasized that an objective test is essential. The drooping of the lower eyelid associated with facial palsy removes the lacrimal punctum from contact with the globe and results in failure of the mechanism of drainage, so that the eye may appear to be swimming in tears when, in fact, secretion is minimal. It was not realized that the nose was involved until the patient caught a cold and noted the absence of secretion on the affected side. The entry "equal" on March 20 only means that the cold had got better and it is not till a week later, at two months, when the right side begins to over-secrete, that we can be sure that recovery has commenced. This eventually settled down and in October, when the patient caught another cold, both sides of the nose reacted in the usual manner.

The figures for nasal temperatures, though they conform to theoretical expectation, are offered with diffidence since this investigation has only been carried out on one case, and it will be repeated if further material becomes available.

1953	Taste	Tears	Nasal Secretion		Intr.Nasal Temp.		Temp.after Pilocarpine		Temp.after Benzedrine		Facial Nerve	
			R.	L.	R.	L.	R.	L.	R.	L.		
31 Jan.	Absent										Complete palsy	Herpes
8 Feb.		Eye dry										
15 Feb.											R.D.	
15 Feb.		Greatly reduced										
17 Feb.											R.D.	
19 Feb.	Absent											Herpes gone
22 Feb.		Almost nil										
24 Feb.				+								Cold
6 March	Absent	Dimin.		+	34	36	34	36	33	33	Complete	
20 March	Absent	Dimin.	Equal		34.5	35	37	36.5			"	
27 March			+									2 mths.
10 April	Absent	Equal	+		35	34			32.5	33.5	"	2½ mths.
8 May	Absent	Slight+	+		35.5	34.5					"	
13 May											Slight movement	3½ mths.
14 June			Equal									
8 July	Absent	Slight+									Marked improve-ment	
21 Oct.			+	+								Cold
18 Nov.	Absent	Equal									Good but not normal	10 mths.

FIG. 1.

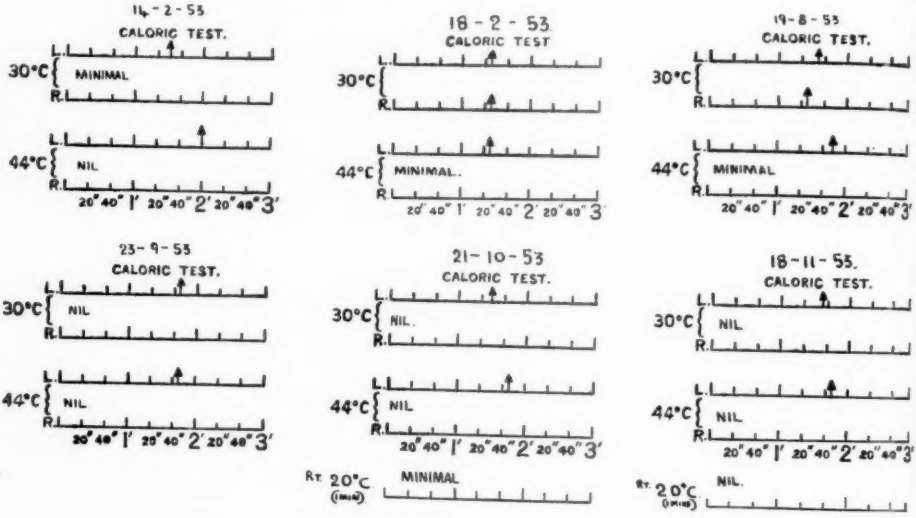
During the period of parasympathetic paralysis, the resting temperature on the right side was lower than on the normal side but when recovery and over-action had occurred the temperature became raised above the normal. The readings obtained after stimulation of the parasympathetic with pilocarpine and of the sympathetic with Benzedrine fall into place if one can assume that a blood vessel is only capable of a certain maximum contraction or dilatation and that, normally, it lies in a mid-condition, being influenced simultaneously in both directions. If, therefore, a vessel which is deprived of its dilator fibres and consequently is near to a state of contraction, is subjected to a dilator stimulus, the effect will be greater than would result from the same stimulus applied to a normal vessel which is nearer to a state of dilatation. On the first occasion, the dose of pilocarpine was small and produced no change on either side, but with a larger dose there was a rise of temperature of 2·5° C. on the abnormal side but only of 1·5° C. on the normal. Benzedrine, producing the opposite effect, is only able to lower the temperature by one degree on the abnormal side where the vessels are already near to full contraction, but lowers the temperature by 3 degrees on the other side. On April 10, when Benzedrine was used for the second time, there is a change in the situation in that the parasympathetic has recovered and is, in fact, over-acting. Now the vessels on the right side are abnormally dilated and react more to a constricting stimulus than do those on the normal side, with the result that temperatures drop 2·5° C. on the right as against 0·5° C. on the left.

I would therefore suggest that in this particular case we must, unless we are prepared to assume the presence of multiple and widely spaced lesions, agree that the ganglion is at fault. Further confirmation is afforded by the order of return of three of the lost functions and the failure of return of the fourth. Taste fibres have their cells in the ganglion, but with the eye, nose and face it is only a matter of fibres passing through or around the ganglion. The secretory fibres to the eye and nose are of much smaller diameter than are the motor fibres of the facial nerve and it is known that small diameter fibres withstand pressure better than do large ones. This all fits in: the nose and eye recover first, in two and two and a half months respectively, the face takes longer, three and a half months, while the taste has not recovered in ten months, and if the cells are destroyed, it never will. There is still the problem of the VIII nerve, which is affected in a curiously selective manner.

The audiograms in Fig. 2 show the complete recovery of hearing, a feature common to all 3 cases, but the vestibular labyrinth behaves very differently. The damage was marked from the first, but after six months it became worse, so that now there is no reaction even to water at 20° C. In the second case, the vestibular damage, though persisting, has not increased.

Shute (1951) describes the facio-cochlear anastomosis as a connexion between the cochlear nerve and the ganglion itself. There is Oorts bundle constituting a pathway between the cochlear nerve and

the inferior vestibular ganglion, and, lastly, the three portions of the nerve and the vestibular ganglia are all closely applied to each other. Since it is known that a neurotropic virus can track in both directions along either sensory or motor nerves, it seems reasonable to accept the possibility of a direct spread to some or all portions of the VIII nerve. It is not, however, so easy to explain the differing fates of the cochlear and vestibular labyrinths. The recovery of hearing must imply that the spiral ganglion escapes and, conversely, the permanent damage to the vestibular apparatus suggests that the vestibular ganglia are involved. It would be most attractive to conclude that the deafness is a secondary and temporary phenomenon resulting from pressure of the swollen ganglia upon the cochlear nerve and capable of recovery. Unfortunately, my first case deals this theory a severe blow



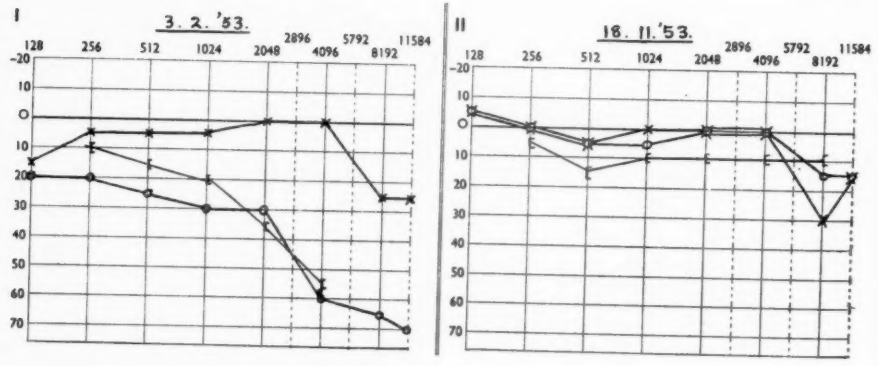


FIG. 2 (*Case III*).

in that, although deafness was present, we did not, admittedly with an incomplete investigation, find any evidence of vestibular damage. Alternatively, it could be held that the lesion of the cochlear division of the nerve is limited to a neuritis which can recover but that, should the infection spread to the vestibular portion, there ensues an additional ganglionitis, which is irreversible. Some virus infections are known to be very patchy in their distribution, but it is difficult to believe that the infection would always die out before reaching the spiral ganglion, and I must own that I am not satisfied with either of these explanations.

These cases present curious anomalies. Only 2 have herpes, but all have a facial palsy. The severity of the palsy has no relation to the extent of the herpes. 2 have permanent damage to the labyrinth

but the third escapes. In fact the only symptom common to all is a deafness that recovers. It would seem that the site or sites of the lesions in this disease are very variable and I feel that it would be no more justifiable to assume that Ramsay Hunt was entirely wrong than it would be to claim that every case can be explained solely on his hypothesis.

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Dr. Wilfred Harris thanked the openers for their scholarly addresses. It was mentioned that some of the cases seen showed symptoms of loss of taste on the tongue and palate which was symptomatic of a case of geniculate neuritis. It was an uncommon syndrome and he had seen it in about 8 cases. Dr. Spillane rightly drew attention to the fact that the diagnosis of geniculate neuritis was not based on post-mortem facts, but the syndrome was so definite that he thought one was not wrong in continuing to call it geniculate neuritis until one knew better.

The first case he saw was over forty years ago at St. Mary's Hospital. There was severe pain in the ear with a bloody discharge from the meatus, and Dr. William Hill, otologist, was not sure of the cause. The hearing apparently was not involved. Dr. Hill syringed out the ear and the result was most agonizing pain lasting for weeks. When he examined the patient himself he found he had a typical rash of herpes on the posterior wall of the meatus and at the junction of the pinna with the scalp, and the actual tympanic membrane was also involved. There was no facial palsy and in process of time the patient recovered.

In another case with a similar syndrome loss of taste was definite. A colleague had told him that he had difficulty in testing a case of taste loss on the palate. The best way was to use an illuminated spatula to hold down the tongue and gently rub a moist swab soaked in a bitter solution on the palate. A good method is to use a weak galvanic current, touch the palate with one electrode when a sensation of a coppery taste will be noticed only on the normal side touched by the current. He had used that many times and was able to demonstrate the loss of taste on the palate in cases of facial palsy before classes of students and medical registrars. There was no question about the loss of taste on the tongue in cases of facial palsy. There was not such a large distribution of taste in the palate as on the tongue and in old people the test on the palate was not very satisfactory.

In 1909 or 1910 at a neurological meeting he mentioned that loss of taste was commonplace in facial palsy and he was jeered at by the Neurological Society members; he could not then understand why because he thought everybody knew that loss of taste on the tongue was common in facial palsy and now it was universally accepted.

Lesions in the geniculate ganglion might or might not be associated with facial palsy. The association might be accidental and muscular palsy applied also to herpes elsewhere in the body. Every now and again one saw it in the abdominal muscles. He had seen a total Erb's palsy of the biceps and deltoid and other muscles associated with a typical distribution of fifth cervical herpetic scarring.

Hunt having carefully described the syndrome in the early 1900s, the speaker remembered that Hunt was associated with a case of Pierce Clark's of tic in the facial region when the man had been suffering violent pain for years in this area. An operation was performed to divide the pars intermedia Wrisbergi and the case was cured. It was a marvellous opportunity for testing the taste function and he wrote and asked Ramsay Hunt what was the effect on taste and he replied that he was ashamed to say that neither he nor anyone else had thought of testing taste.

Herpetic pain could continue for years, it was an agonizing symptom and he knew of the case of a man suffering from shingles followed by severe long-continued herpetic pain; all sorts of treatments were tried, and somebody with more wit than brain suggested cutting off the whole area of skin affected by the scarring of the herpes. The man consented to this being done, he bore the pain of the incision without any anæsthetic, but the post-herpetic pain continued, and the man shot himself.

Mr. Norman A. Punt wished to report briefly 2 cases which suggested that the herpes zoster virus might affect various neural pathways at random, and that clinical estimation of its routes of spread and distribution should be accepted with reserve.

A man presented with complete left facial paralysis and diminished taste sensation; there were herpes vesicles over the postero-superior part of the tympanic membrane, meatus and neighbouring pinna. There were also a left palatal paresis, recurrent nerve paresis and possibly cricopharyngeus paresis. There were no mucosal vesicles. He had only transient deafness, due to the skin lesions.

A woman complained of pain in the right ear; the skin behind the ear was a little reddened, but there was no other ear lesion and no deafness. She developed a complete right facial paralysis with diminished taste sensation. Injection and herpes vesicles appeared and were confined to the right side

of the soft palate and posterior pharyngeal wall. There was a Horner's syndrome, and also nausea and giddiness which were believed to be vagal in origin, no cochlear or labyrinthine dysfunction being demonstrable.

Mr. A. Laskiewicz said that the topography and vascularization of the fallopian canal could be proved by the following method: a very thin metal wire, or any strong contrast medium, should be introduced into the lower end of the fallopian canal on the dried temporal bone. A radiograph taken in the Stenvers position and the lateral oblique position showed the course of the named canal which could be distinguished as four principal types: (1) the nearly right angular form about 75%; (2) the arched regular form nearly 25%; (3) the wavy form, 3%; and (4) the double arched form, 1% in which the point of junction of both arches corresponded nearly to the region of the geniculate ganglion.

The vascularization of the fallopian canal and the facial nerve was given by the stylomastoid artery, the stem of which was surrounded by the auricular branch of the vagus nerve and in cases of aneurysm of the lower part of this artery there was often complete anæsthesia of this branch. Secondly, small branches of the arteria meningea media and auditiva interna dealt also with the blood supply of this canal. The veins flowing off consisted of a formation of a fine venous plexus joined closely with the surrounding bony vessels. The stream was directed mainly towards the petrosal superior sinus and the vena auditiva interna.

In 2 cases of facial nerve palsy with herpes zoster cephalicus in men aged 41 and 46, the main complaints were of giddiness with hardness of hearing, burning pains in the margins and apex of the tongue, and unilateral facial nerve palsy. In both cases herpetical blisters were very evident in front of the auricle and around the entry to the external meatus; in the first case also on the right side of the palate. In both cases one was dealing with a considerable decrease of the sense of smell and parosmia, e.g. the smell of eau-de-Cologne was taken as the smell of oil or petroleum.

As to the sense of taste, there was parageusia, with permanent salty or bitter taste, unilateral hypogeusia for sweet or sour substances, besides a lowering of the feeling sensation on the given side. After administration of chloramphenicol 0·5 gramme three times daily for four days, supported by injections of vitamin B_1, these disturbances disappeared within three weeks, and only unilateral hardness of hearing remained.

Mr. Terence Cawthorne said that a matter of prime importance in dealing with cases of facial paralysis, was a full exploration of the various functions of the facial nerve. Besides enquiring into the state of the facial musculature it was necessary to test the ability to taste and to lacrimate. Hearing was also often mentioned because it was thought that paralysis of the stapedius muscle gave rise to sensitivity to loud low-pitched sounds. He had rarely noted this though he thought that at times it might occur. The reason why it was so rare was that the protective function of the stapedius muscle when it was paralysed was taken over by the tensor tympani which was supplied by the V nerve.

He had found that it was always advisable to test lacrimation. There were certain cases which superficially were like an ordinary Bell's palsy but in which lacrimation was impaired. There might also be involvement of the VIII nerve as well but no herpes. At one time he had thought that impairment of lacrimal secretion always meant a dry eye but this was not so, because the eye could be kept moist by secretion from other glands in the conjunctiva.

He had operated on one case of herpes facialis in which the face remained paralysed a year after the disease appeared. He exposed the nerve right forward to the geniculate ganglion and it was observed that the nerve in the neighbourhood of the geniculate ganglion was discoloured and swollen. Within two months of the operation there was a partial return of facial movements.